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## The Use of Radiology in Predicting Difficult Labour*

BY

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LECTURE I: Introduction; Technical Considerations in Pelvimetry and Cephalometry.

### INTRODUCTION.

AFTER paying tribute to Dr. J. T. Ingleby, physician and accoucheur in Birmingham in the earlier part of the eighteenth century, and comparing the incidence and importance of pelvic contractions in his day and in this, the lecturer proceeded as follows:

Nine years ago, when the Nuffield Unit of Obstetrics and Gynaecology was founded in Oxford, the opportunity arose of undertaking a comprehensive investigation of the value of radiology in forecasting the course of labour, and to this end, I was able to have incorporated in the new labour ward suite a self-contained X-ray room of generous size. Hitherto, it seemed to me, the use of radiology for antenatal and intranatal diagnosis had suffered from two faults; firstly, there had too often been a lack of co-operation between the radiologist and obstetrician so that neither fully appreciated the needs and difficulties of the other; and secondly, there was—and, I believe, still is—too much reliance placed on what might be termed an impressionistic interpretation of the radiograph, with opinions based on general appearances rather than on precise data concerning the dimensions of the maternal pelvis on the one hand and of the foetal head on the other. On these lines there was little hope of scientific progress, nor was it possible for the methods, such as they were, to be adequately explained in writing or easily taught by word of mouth.

In this investigation I resolved to undertake the technical side of the radiological work myself—not because I consider that obstetricians in general should so engage, but because I wished to make a serious study of the various methods of pelvimetry and to learn for myself their relative merits and the possible sources of error. Moreover, in the proposed experimental work it was necessary to know beyond doubt that the radiographs were secured with the patients correctly positioned and with the necessary adjustments accurately made. Nearly 800 patients have now passed through my hands, and although the combined rôle of radiologist and obstetrician has been heavy, it has enormously added

* The first of two Ingleby Lectures delivered at the University of Birmingham, May 1946. The second lecture, "Forecasting the course of labour," will appear in the next issue of the *Journal*.

to the interest and, I believe, to the value of the work. It has also enabled me to develop several small but useful modifications to the standard method of pelvimetry which will presently be described.

I now welcome this opportunity of presenting an account of this long-term research and, particularly, of placing before you, for what it is worth, a new system by which the obstetric value of the pelvis may be assessed with relative ease and with a fair degree of accuracy.

## Technical Considerations.

To discuss in detail the various radiological methods of pelvic examination* is beyond the scope of these lectures nor is it possible to do more than acknowledge the magnificent work of Caldwell and Moloy*, D'Esopo[10] and others on the variations of pelvic formation and their significance. It is enough to say of 3 or 4 reliable systems of pelvimetry I have no doubt that for routine work in a busy hospital the isometric method—associated particularly with the name of Herbert Thoms[7] of New Haven—is the first choice. In it a scale is incorporated in each film so that the obstetrician himself can measure what he will, and can do so without need for arithmetical calculation or reference to correction tables. Moreover, as will be shown, certain simple pieces of apparatus can be constructed, and fixtures added to the X-ray plant, by which the taking of the films is greatly simplified. The methods are these.

*Lateral projection.* The lateral view of the pelvis is by far the most important of any single radiological examination, both on its own account, and because information gained enables the patient to be correctly positioned for subsequent examinations.

The radiograph is obtained with the patient standing erect, and with the X-ray tube at not less than 4 feet range from the film. If a stationary (Lysholm) grid is used, 4 feet 3 inches is a convenient distance; if the thicker Potter-Bucky grid is used 4 feet 6 inches should be the minimum. I have found it possible to simplify the technique by attaching to the upright screening stand two movable wooden pegs against which the patient presses her anterior superior iliac spines. One of these pegs is attached to, and moves up and down with, the film-cassette holder; the other has an independent vertical movement to suit the height of the patient (Fig. 1); the precise size and position of

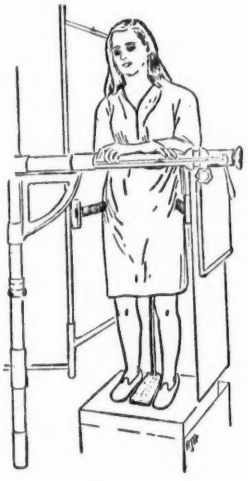
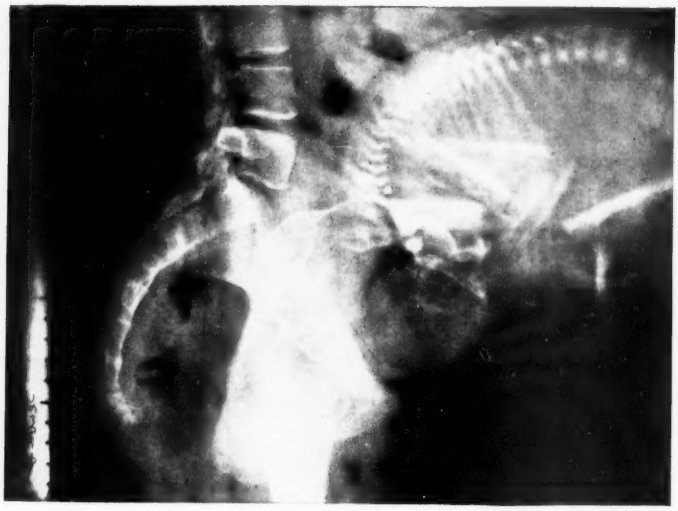


Fig. 1.
Position for lateral pelvimetry showing the pegs against which the patient presses her anterior-superior iliac spines (see text).

the pegs have in the first instance been carefully calculated to ensure the correct positioning of the average patient. By this simple expedient three of the bugbears of lateral radiography are at once eliminated: the patient assumes the true lateral position, she remains motionless during exposure, and the X-ray tube is automatically positioned over a selected centre of the pelvis (ideally the spines of the ischium). There is the further advantage that, with the patient immobilized, the milliampereage may be reduced and exposure prolonged, thus greatly lessening the strain on the tube. After positioning, a metal rod mounted on a firm stand is placed between the patient's legs

* See references, 1, 2, 3, 4, 5, 6, 7, 8 and 9.



*Baillière, Tindall & Cox*

PLATE I.

Lateral pelvimetry, showing measuring-rod in position.

C. M.

Acknowledgment is made to Messrs. Baillière, Tindall & Cox for permission to reproduce Figures 1, 2, 3, 4, 6, and Plates I, II, III, V, VI, VII, VIII and IX from the new edition of Munro Kerr's *Operative Obstetrics*, now in the press.

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so that a centimetre measure rests alongside the cleft of the buttocks. A scale equally magnified with the pelvis in the sagittal plane is thus impressed on the resulting film (Plate I).

If the patient has been correctly positioned the resulting radiograph should show two acetabulae nearly superimposed, and the spines of the ischium quite superimposed. The erect standing posture makes exact positioning much easier, for a sideways tilting of the pelvis—a common fault in lateral radiography—is thereby reduced to a minimum. Even if the patient is in labour she can usually be encouraged to stand; but if that is not possible, use can be made of a positioning apparatus similar to that already described, but adapted for the horizontal lateral position.

The lateral picture gives exact information of the brim conjugate which no other view can give. It also shows: (1) the true, and the false promontory (if present); (2) the inclination of the pelvic brim; (3) the relation of the foetal head to the brim, and the degree of the engagement; (4) the bi-parietal diameter, or some other diameter from which the bi-parietal may be estimated; (5) the length and shape of the sacrum; (6) the size and shape of the sacro-sciatic notch; (7) the length of the lower antero-posterior diameter (from the lower inner margin of the pubic symphysis to the tip of the sacrum); (8) the length of the posterior sagittal diameter of the outlet (from the midpoint of a line joining the ischial tuberosities to the tip of the sacrum).

*Supero-inferior projection.* A second picture is a supero-inferior, or "plan", view of the pelvic inlet, and is obtained by placing the patient on the X-ray table in a reclining position (Fig. 2).

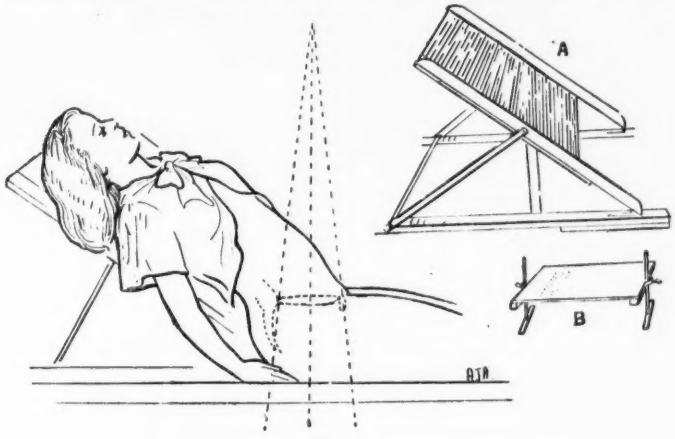


FIG. 2.
Position for supero-inferior projection pelvimetry

This method of obtaining the outline of the pelvic brim is well established, but unless precautions are taken to ensure that the plane of the brim is parallel to the table (or, alternatively, that suitable compensation is made for any angulation, as in Thoms's original method), results may be misleading. It is often stated that the patient has been correctly positioned if in the resulting picture the superior and inferior pubic rami are superimposed, thus obliterating any view of the obturator foramena. In general, this is true, but there are types of pelves whose conformation is such that the superior and inferior rami do not become superimposed even with correct positioning; this is seen especially when there is a wide pubic arch. The

pelvic brim is usually rendered parallel, or nearly parallel, to the table when the back-rest is at an angle of 35 degrees, and the patient's lumbar region is in a position of lordosis.

For greater accuracy the following method has been developed. When the previous lateral radiograph was made, a small metal marker was fixed to the skin over the sacrum at the approximate level of the posterior superior iliac spines; in the resulting picture the angle formed by the lines joining the upper margin of the symphysis pubis to the marker on the one side, and to the posterior extremity of the brim on the other, was measured. A series of half-circle wire hoops is now at hand; each hoop is shaped to touch the skin marker behind, and the upper border of the symphysis pubes in front

40 inches distant from the film (I use 47 inches) and centred 2½ inches posterior to the upper margin of the symphysis pubis. After the exposure the patient leaves the table and the scale is impressed on the film in the following manner. A thin lead sheet, perforated at centimetre intervals, is placed above the table at a height corresponding with the position previously occupied by the brim of the pelvis. (This height is conveniently determined at the time of the first exposure by recording with a drop-line the distance from the X-ray tube to the upper border of the symphysis, allowing for any table-sag caused by the patient's weight.) A second flash exposure is now made, and the centimetre marks, correctly magnified, are thus superimposed on the film (Plate II).

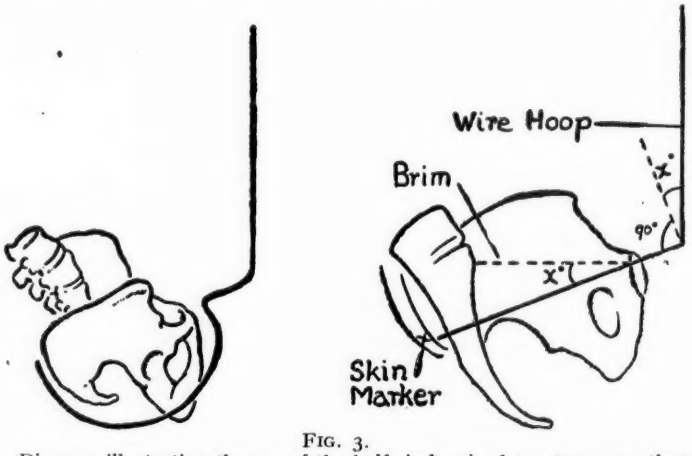


FIG. 3.
Diagram illustrating the use of the half-circle wire hoop to ensure that the pelvic brim is rendered parallel to the top of the radiographic table (see text).

From the front of the hoop an arm extends upwards making an angle with the vertical which, in different hoops, varies from 10 to 35 degrees. When the supero-inferior radiograph is to be made, the hoop with an angle corresponding to the angle previously measured on the lateral radiograph is selected, and is applied to the points mentioned; the patient—or, more accurately, the patient's pelvis—is then positioned until the arm of the wire hoop points vertically upwards. With the pelvis in this position the brim is necessarily rendered parallel to the table (Fig. 3).

The exposure is made with the tube at least

In recent years, Thoms[11] has slightly altered his method. As in the description given above, he now aims at positioning the patient so that the pelvic brim (and consequently also the perforated plate) is always parallel to the table top. Instead of the uniform centimetre scale, it now becomes possible to introduce a series of scales (Plate III). One of these is a true centimetre scale and is used as before for the measurement of the brim. When, however, landmarks at levels below the brim

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PLATE II.

Example of supero-inferior projection pelvimetry. (In this case there is markedly "anthropoid" brim.)

C. M.

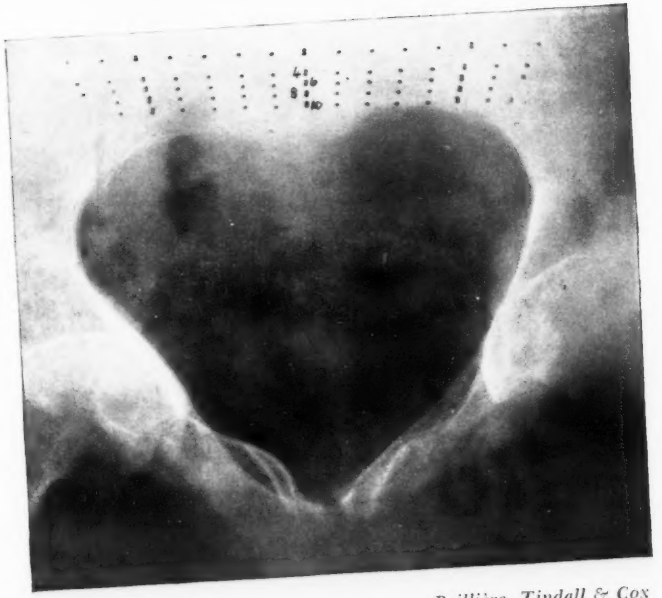

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PLATE III.

Example of supero-inferior projection pelvimetry showing the use of the multiple scale. (In this case the brim is markedly wedge-shaped.)

C. M.

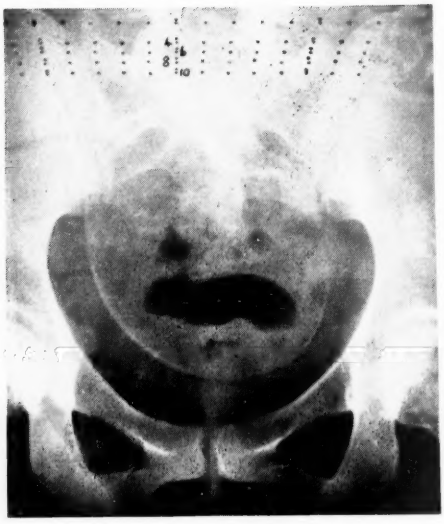

PLATE IV.

Modified position for measuring, in a patient at term, the available transverse diameter of the brim, and the bi-spinous diameter.

C. M.

are to be measured—for example, the bi-spinous diameter—the difference in level from the brim must first be determined by reference to the lateral radiograph, whereupon the appropriate supplementary or "corrected centimetre" scale* shown in the supero-inferior radiograph can be selected for the measurement in hand. The method removes the necessity for mathematical calculation or reference to correction tables, and it thus greatly reduces the work necessary for obtaining the measurements from the film. It has definite advantages over Thoms's earlier technique.

*Modification for patients at term.* If the woman is near term, the radiograph obtained by the above method tends to be of poor quality; although the brim can be discerned, the ischial spines—important landmarks—are usually obscured. Better pictures are obtained if the patient is examined in the dorsal position with a pad under the small of the back to cause lordosis. In this position the ischial spines are more easily identified and the bi-spinous diameter measured, although the shape of the brim is lost because of the considerable foreshortening of its antero-posterior dimensions (Plate IV). This disadvantage is however not so grave as might be supposed, for, by calculation, the particular transverse diameter which has most obstetric significance—the *Available Transverse* as I like to call it—can still be measured with fair accuracy. This is the diameter that intersects the conjugate at mid-point; its significance will be discussed in a later section.

When the patient is in the dorsal position the measurement of any brim diameter is a difficult matter. The available transverse diameter is identifiable only because of the fortunate finding that its position very closely corresponds with that of a line joining points 2 mm. posterior to the posterior acetabular margins. A small correction is necessary if the posterior sagittal diameter is unusually short (the so-called "android", or wedge-shaped brim), or unusually long. Both these conditions can be diagnosed from the lateral radiograph by noting the position of the posterior margins of the acetabular cups relative to the sacrum—near in the one case and distant in the other. In the former, the available transverse diameter occupies a position 2 or even 3 mm. further forward than the position above stated, and in the latter it is 2 or even 3 mm. further back. The scale is introduced as in the standard method. The measurement of the level of this diameter below the top of the pubis (and hence below the level of the scale) is explained in connexion with Fig. 4. No claim of high accuracy can be made when this rough and empirical method is used; nevertheless, when the measurements obtained by the two techniques of brim pelvimetry are compared it is seldom that a discrepancy of as much as 2 or 3 per cent is

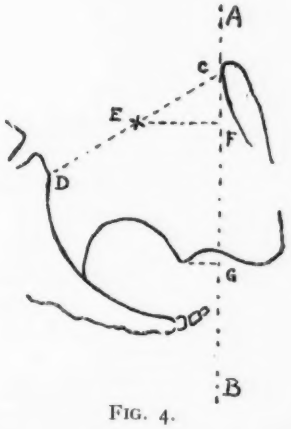


FIG. 4.

Method of measuring the depth of the available transverse diameter of the brim from the top of the pubes, and hence from the level of the scales. AB is drawn to mark the position of the tip of the coccyx relative to the symphysis pubis as seen in the antero-posterior radiograph. From mid-point E of the conjugate CD a line EF is drawn vertical to AB. CF then gives the required measurement.

* The supplementary scales are plotted in the first place by dummy experiment; once made they are sufficiently accurate for all ordinary clinical use so long as a constant target-film range is employed.

encountered. In practice, the information given by the second method is therefore usually sufficient for the purpose in hand.

There is another objection to the use of the standard method when pregnancy is far advanced. When the patient is placed in the reclining position the fundus of the uterus is, relative to the pelvis, very close to the X-ray tube. Now, since the intensity of radiation varies inversely with the square of the distance, it follows that the foetal part occupying the uterine fundus—normally the breech—receives an excessively heavy exposure, and one which, for all we know, may be harmful to the foetus. This is avoided by the modification described.

*Pubic arch measurement.* The third picture concerns the pubic arch. In the usual antero-posterior view of the pelvis the shadow of the arch is greatly foreshortened, and its measurement is then little more than guesswork. In the Chassard-Lapine[12] technique the patient sits on the film casette and bends well forward while the tube is centred vertically over the ischial tuberosities. By this means the pubic arch is made to lie approximately parallel to the film, and distortion is almost eliminated.

The following modification has been evolved which is more convenient for the pregnant woman. The patient sits on a specially constructed box in which there is an oblique slot to hold a cassette for 6 × 4 inch-size film (Plate V). Matters are so arranged that when she assumes a comfortable sitting posture the ischial tuberosities slide into a groove, thus correctly positioning the pelvis and, at the same time, ensuring that the pubic arch lies approximately parallel to the plane of the film. If desired, the patient can be still more accurately positioned by an adaption of the marker technique already described; but in practice this has not been found necessary. Exposure is made from behind, with the X-ray tube obliquely tilted so that its rays impinge on the film at a right angle. The smallest possible diaphragm is used in the X-ray tube to obviate the need of using a stationary grid to cover the film (Plates VI and VII).

There are various ways of measuring the radiograph of the arch. The most obvious is to measure the distance between the ischial tuberosities. Unfortunately, these points are indefinite, and some arbitrary means must therefore be adopted for their identification; thus, Rohan Williams recommends measuring from the lateral margins of the obturator foramina. Another method is to place a circular disc, representing the size of the foetal head, in the span of the arch, and then to measure the wasted space between the foetal head and the lower border of the symphysis pubis; by this means a useful indication is obtained of the obstetric value of the arch. This method has been tried in the Oxford investigations, and has also been developed independently by Dewar of Dumfries, and Morris and Whittaker of Ayr. The simplest method is to measure the arch-angle. Unfortunately, the limbs of the arch are often curved and this has led to varying definitions of the arch-angle by different workers. In my own work I have adopted the definition urged by Nicholson. The lower border of the symphysis is identified, and a spot selected exactly between the two pubic bones; from this point lines are drawn to touch the pubic rami where they project furthest inwards—usually in the neighbourhood of the ischial tuberosities. The angle between those lines is then measured.

*Summary.* By those 3 radiographs all the important pelvic measurements can be determined. In each picture the need for arithmetical calculation has been eliminated; the methods are, in short, devised to reduce the examination to the simplest possible form compatible with the accur-

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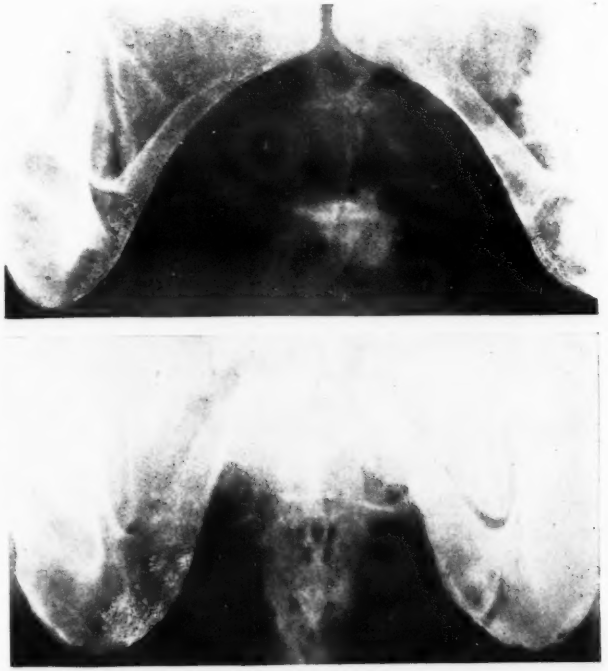
PLATE V.

Special stool for pubic arch pelvimetry, showing position assumed by the pelvis.

C. M.



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PLATES VI and VII.

Examples of pubic arch pelvimetry.

C. M.

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PLATE VIII.

Example of cephalometry in the case of a breech presentation.

C. M.

acy required for clinical work. Here it may be added that there is evidence that the pelvic dimensions themselves vary slightly according to the position of the patient, for example, whether erect or recumbent, and it is therefore important that the technique used should be constant.

*Time of examination.* The examinations are best made in the last weeks of pregnancy, partly because it is unwise to subject an early embryo to heavy and repeated radiation, and partly because the size of the foetal head and its relationship to the brim can then be estimated. In the postnatal period pelvimetry may again be of value, for an explanation may then be forthcoming for some unexpected difficulty that has arisen during the course of labour, and the information so obtained may give material help in deciding treatment on a future occasion.

## Cephalometry.

Thus far pelvimetry only has been considered; let us now turn to cephalometry. Obstetric disproportion means an unfavourable relationship of the foetal head to the maternal pelvis, and it is therefore illogical to study the one without the other. Now, in size, shape and plasticity, foetal heads vary to a surprising extent. Further, the foetal head is an awkward object to measure by X-rays, particularly as it sometimes lies free above the brim and inclined to one or other iliac fossa. But the difficulties are not so great as to make cephalometry worthless; and although precision cannot always be attained, it is usually possible to state a measurement below which the shortest diameter of the skull (the suboccipito-bregmatic, or the biparietal) must lie. This in itself is information of considerable value.

The shortest diameter of the skull is chosen for this work because, as pointed out by Reece,[3] it is the one always seen on the radiograph, whereas the longest diameter is revealed only if the long axis of the head happens to lie at right angles to the direction of the rays.* The measurement is generally obtained from the lateral picture, but if the view of the head is unsatisfactory, help may also be obtained from examination of the supero-inferior picture of the pelvic brim, allowance being made for any difference of level of the required diameter of the head from the level of the centimetre scale. In the case of a breech presentation, cephalometry is conveniently made with the patient standing erect, and with the tube at 4 feet 6 inches distance from the film. The abdomen is palpated and the patient positioned to bring the foetal head into a "tangential" position; the patient herself then holds the centimetre measure directly over the mid point of the head (Plate VIII).

If the biparietal diameter can be clearly seen—and very often it is—one is safe in stating its measurement. Next best is the suboccipito-bregmatic diameter. If, however, an oblique diameter only is visible, one is left in some uncertainty regarding the size of the head, and all that can be said is that the biparietal diameter will be *less* than the visible shortest diameter. Exceptions to this are very few. Reece assumes that the biparietal and the suboccipito-bregmatic diameters are equal. In a long series of measurements I have found that this is not invariably true; sometimes—especially in the case of soft skulls—the suboccipito-bregmatic is greater than the biparietal diameter (rarely by as much as 5 millimetres); while sometimes—especially in the case of well-ossified skulls—there are decided parietal bosses causing the bi-parietal to exceed the suboccipito-bregmatic diameter (again rarely by as much as 5 millimetres). For the present purpose it is unfortunate that there should be any uncertainty about these measurements; but there does not appear to be any other simpler method of

* Compare the shadow of an egg. The long axis is shown only when the egg is in a certain position, the shortest diameter is shown in every position.

cephalometry, and we must therefore continue to use the bi-parietal diameter as the best available indicator of head size.

In my work I have, so far as possible, always checked the radiographic estimation of head size by clinical measurement after birth, and after moulding has passed off. Measurement is made by lightly grasping the head from side to side and measuring the bi-parietal diameter with engineers' callipers; the span is then read off on a ruler. Obstetric callipers are much too inaccurate for this work. Personal measurement is necessary, for different observers may not agree to within 1, 2, or even more millimetres of the exact dimension. This is partly because of the inconstant pressure applied to the head, which will, in the case of a soft mouldable head, appreciably alter the readings.

*Growth of the foetal head.* If radiographic examination has been made before term, it is necessary to allow for the subsequent growth of the head. Scammons and Calkin[13] state that this averages 2.5 mm. (1/10 of an inch) per week. My own practice is to allow 2 mm. per week. I am influenced in selecting this smaller figure because of the observed rate of growth of the infant's head in the neonatal period (Fig. 5).

*Moulding of the head.* Moulding of the head is, of course, a matter of highest importance. When the head is measured at birth, and again 24 hours later, it is usual to find that the biparietal diameter has increased by 1 or 2 millimetres. Sometimes the difference may be 4, 5, or even more millimetres; but in these cases the head is less well ossified than normal, and can be readily altered in shape even by finger pressure (Plate IX).

This matter of moulding is held by some to nullify the value of cephalometry and to frustrate any serious attempt at predict-

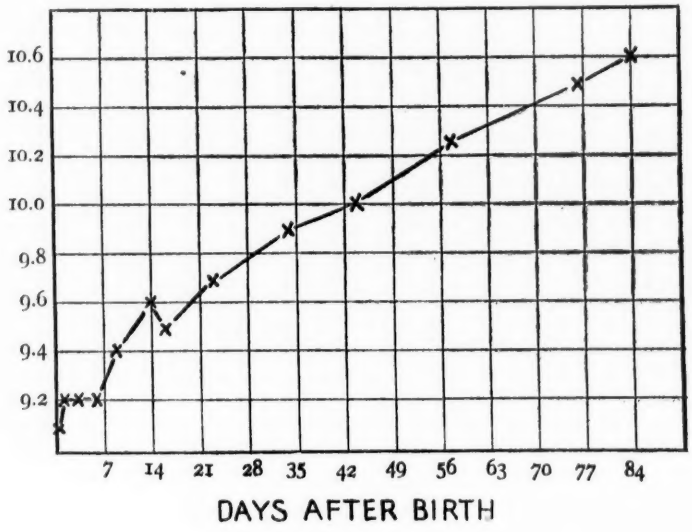


FIG. 5.

Growth of an infant's head after birth (bi-parietal diameter in centimetres). The slight irregularity on the 14th day was presumably caused by an error in measurement.

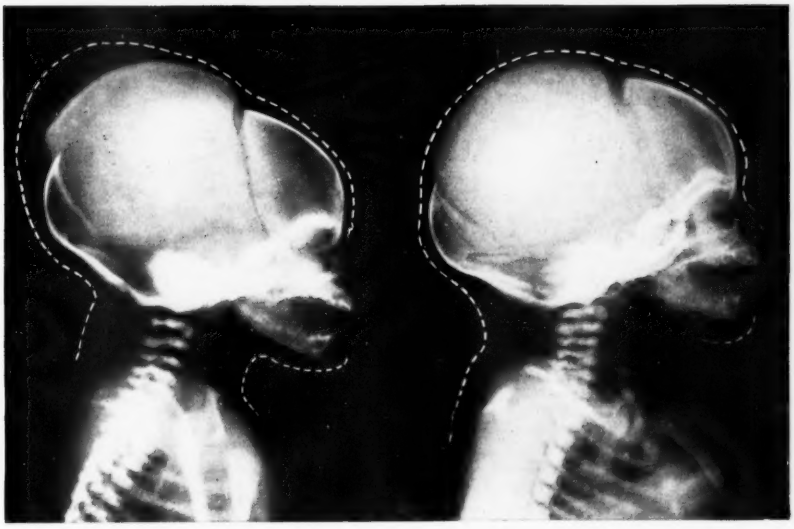

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PLATE IX.

Left: Moulding of an infant's head half an hour after delivery. Right: The same infant 3 days later. (The skin outline, lost in reproduction, is indicated by dotted lines.)

C. M.

ing the course of labour. I do not agree with these sweeping statements. It is common knowledge that good moulding will greatly facilitate the progress of labour in a case of borderline disproportion. But there is another side to the question. While moulding will at times enable a seemingly impossible obstacle to be overcome, remarkable happenings of revealing pelvic type, radiology will often indicate when moulding will, and when it will not, be an effective factor. Again, moulding is safe only when it is moderate in degree; and there is a point beyond which it endangers the foetal life. It is often effective in the case of the small foetus, but is less effective or safe in the case of the post-mature foetus with a well-

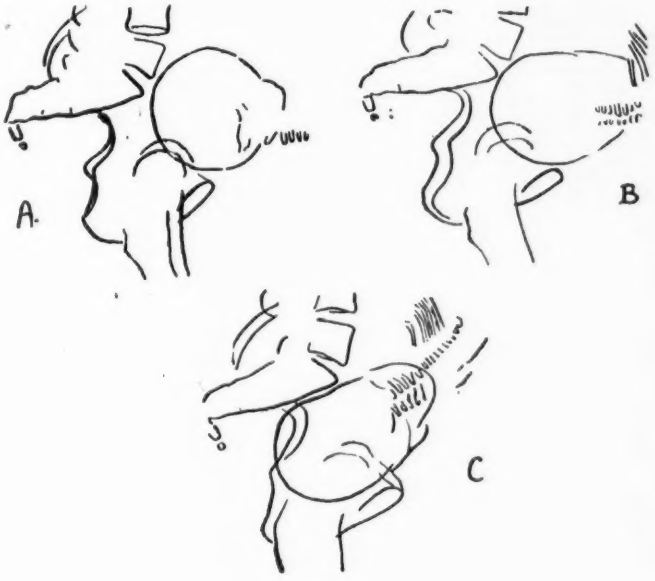


FIG. 6.

Tracings of radiographs showing progress of labour in a rachitic flat pelvis with obstetric conjugate of 8.3 cm. (3.3 in.).

A. Before labour. B. Early in labour (11 a.m.). C. Late in labour (3.30 p.m.). Delivery was spontaneous after a labour of 22 hours. The baby weighed 6 lb. 11 oz., the bi-parietal diameter measured (approximately) 8.8 cm.

this nature are encountered almost exclusively in connexion with a pelvis that is contracted in but one dimension, as for example, the rachitic pelvis with its flat brim (Fig. 6). Moulding is not so conspicuously effective in enabling the resistance offered by the generally-contracted pelvis to be overcome. Now, by the ossified head, or with a biparietal diameter of 9.5 cm. or more. To some extent, the degree of danger likewise depends on pelvic type, being least in the rachitic with its one-dimensional compression, and most in the generally-contracted pelvis with its circumferential compression.

When one attempts to predict the course

of labour one assumes that reasonable moulding will take place; but for the reasons stated it is unwise to rely on a reduction of more than 2 or 3 millimetres in any dimension. In doubtful cases it is an advantage to repeat the lateral examination during labour and to observe the degree of moulding attained. But caution must be observed; safe delivery for the mother does not necessarily mean safe delivery for the baby, and foetal death may result from protracted labour even if delivery is spontaneous.

## ADDENDUM.

### *A Comment on a Recent Criticism of Brim Pelvimetry.*

A comprehensive experimental study of radiological pelvimetry has recently been made by O. S. Heyns[14] of Johannesburg. His paper covers a great deal of ground and is an important, if controversial, contribution to the subject. His findings are of great interest and many of them will be generally accepted; some of his statements, however, I have not been able to confirm.

Heyns states that the "brim" outline shown in supero-inferior radiographic projection does not represent the true anatomical brim, but the outline of the pelvic wall as some indefinite distance below the brim. This applies to the lateral walls which, in consequence, represent no particular anatomical landmark and are therefore of little value for measuring the transverse diameter. ("... the greatest transverse diameter of the brim cannot be found, and we submit that it is not possible by any method, stereoscopic or otherwise." Also: "the greatest transverse of the brim obtained from A.P. films is in the region of 7.5 mm. shorter than on the pelvis, the range being from 5 to 10 mm."

If Heyns's contention is correct it seriously undermines the basis of the second method of pelvimetry, and makes the radiographic measurement of the important transverse diameter a highly uncertain procedure.

In my early experimental work I compared the results of stereoscopic pelvimetry with isometric pelvimetry and became aware of the fallacy which Heyns now stresses. I was, however, satisfied that the difference between the transverse diameter as shown in supero-inferior projection and the transverse diameter found on actual measurement of the dried pelvis was too small to be of practical importance. In view of Heyns's findings it was necessary to investigate this matter afresh. Using all the dried pelves available to me (eight) I attached a series of lead shot around the anatomical brim and photographed the pelvis according to the method described in this paper. The difference between the transverse measurement as determined by the position of the shot, and the transverse measurement as determined by the radiographic appearance of the brim margin was in some cases barely measurable; in others it was definite, but in no case did it amount to as much as 2 millimetres. This applied also to the comparison of the radiographic with the direct pelvimetry measurements (Plate X).

I am therefore at a loss to explain why Heyns should find such a considerable discrepancy between the radiographic and the true transverse diameter. The small discrepancy which is certainly present will, of course, become magnified the nearer the tube is brought to the pelvis. In my work I use a standard tube-film distance of 47 inches, and anything appreciably shorter than this is, in my opinion, undesirable. Heyns appears to use a distance of 40 inches, which may give a partial explanation of his different findings. But another explanation is possible: Heyns may select, as the outline of the brim, the innermost margin of any bone outline seen on the film. This, however, would be unreasonable, for care must always be taken to identify the brim margin as it leaves the sacrum and to follow its curve as it crosses the bone mass of the ischium with its projecting spines.

Heyns is also severe in criticism of certain other matters pertaining to the Thoms's technique; for example, Thoms's proposal to measure the depth of the ischial spines from the brim-level by use of lateral pelvimetry. While accepting the theoretical basis of the criticism, I do not concede that an uncertainty affecting the subsequent reckoning of the required diameter to the extent of a 1 or 2 per cent error need invalidate a method of pelvi-

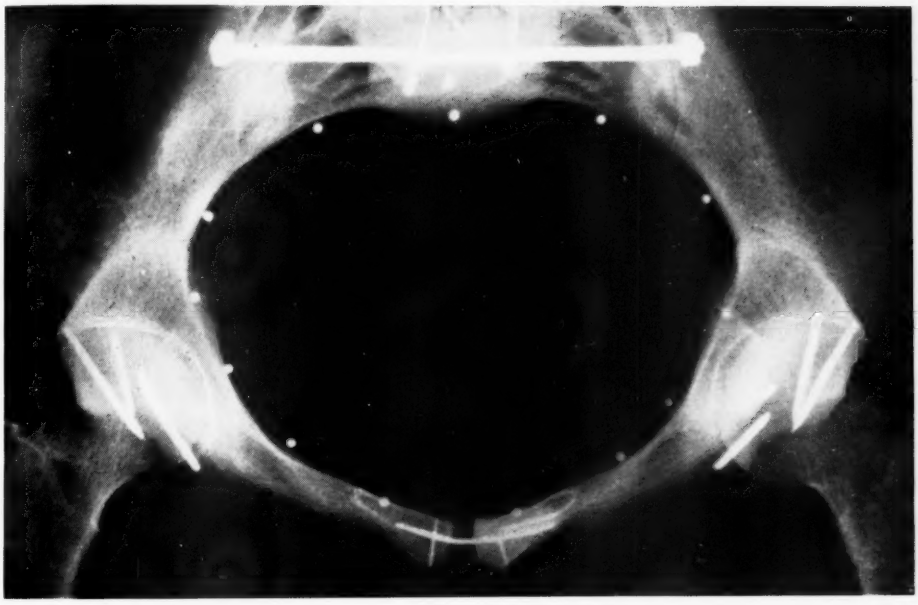

PLATE X.

Radiograph of a dried pelvis showing the close correspondence between the radiographic outline of the lateral portions of the brim and the anatomical brim outline as indicated by the position of the lead shot.

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metry which has the other great advantages of simplicity and convenience. So, too, with the criticism of the radiographic measurement of the pubo-sacral diameter and the alleged uncertainty of locating its anterior end-point. The lower antero-posterior diameter (as it has been called in this paper) and its end-points have already been defined. Only on rare occasions have I found any difficulty in locating the anterior end-point on the radiograph, and then any error has probably been well within the range of ± 2 mm. In experiments on the dried pelvis this point has been located with a margin of error of less than ± 1 mm.


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## The Nutrition of Expectant and Nursing Mothers in Relation to Maternal and Infant Mortality and Morbidity

(The People's League of Health)

In July 1935 the People's League of Health appointed a special committee to consider the influence of the nutrition of expectant and nursing mothers on maternal and infant mortality and morbidity. The Committee consisted of: Professor James Young (British Postgraduate Medical School), Chairman; Miss Margaret Basden (Mothers' Hospital, Salvation Army); Professor F. J. Browne (University College Hospital); Professor Amy Fleming (Royal Free Hospital); Dame Louise McIlroy (Thorpe Coombe Maternity Hospital); W. C. W. Nixon (St. Mary Abbots Hospital, L.C.C.), Medical Secretary; W. H. F. Oxley (East End Maternity Hospital); L. Carnac Rivett (Queen Charlotte's Hospital) and James Wyatt (St. Thomas's Hospital); and the following: H. Davis, P.H.D., P.H.C. (Pharmacist, U.C.H.); Professor J. C. (now Sir Jack) Drummond (Professor of Biochemistry, University College, London); Miss Letitia Fairfield, M.D. (Senior Medical Officer, L.C.C.); W. T. Russell, F.S.S. (Statistician, London School of Hygiene); Miss Jean Wishart, S.R.N. (Queen Mary's Maternity Home) and Miss Olga Nethersole (Founder and Honorary Organiser, People's League of Health).

The League had the co-operation of 10 London Hospitals: East End Maternity Hospital; Hammersmith Hospital (L.C.C.); Mothers' Hospital (Salvation Army); Queen Charlotte's Hospital; St. Mary Abbot's Hospital (L.C.C.); St. Thomas's Hospital; Thorpe Coombe Maternity Hospital; University College Hospital; Queen Mary's Maternity Home (Hampstead) and the Royal Free Hospital.

Three commercial firms—Messrs. Vitamins, Ltd.; Crookes Laboratories and and Roche Products Ltd.—supplied the vitamin and mineral elements required, free of charge.

The Committee issued an Interim Report in 1942, which was published in the *British Medical Journal*[1] and the *Lancet*.[2] The following paragraphs taken from that Report explain the objects and the nature of the investigation:

> The main investigation, which was carried out from March 1938 to the end of 1939, was planned to show whether additions of vitamins and minerals to the food would benefit the course of pregnancy and labour and the newborn child. In order to obtain some information concerning the type of diet consumed by the group of women to be studied, an inquiry was made among expectant mothers attending four of the hospitals which collaborated in the test; these patients included some of the women enrolled in the investigation. It was not possible to make a detailed dietary survey, but nearly 1,000 women filled in questionnaires recording the food they had eaten during a week. This was at best a rough and ready method of assessing food consumption, but there were good reasons for believing that it would give some evidence of the nutritional level of the women during the experimental period. A scoring system was adopted by which arbitrary values were given to express the daily consumption of the more important foodstuffs, such as milk, butter, wholemeal bread, fresh vegetables, fatty fish, fruit, eggs, et cetera. By making a sum of the weekly score for appropriate foods, approximate estimates could be made of the intakes of first-class protein, vitamins, minerals, et cetera, while from a general summation a picture of the diet as a whole was obtained. This procedure was sufficient to reveal

any well-marked deficiencies in the diet. A somewhat similar scoring system has recently been found of great practical utility in nutritional investigations in Toronto.

Analysis of the records showed that, in general, there was no well-marked deficiency of first-class protein among any of the women answering the questionnaires. As regards minerals, a shortage of calcium was noted in about 70 per cent of the women, most of whom were consuming insufficient milk and cheese. Iron deficiency was even more serious, only 2 per cent of the women having a satisfactory intake. As regards vitamins, the deficiency of A was the most common, this being anticipated from comparison with other pre-war data. Rather more than half of the women were taking less vitamin A than they required. Generally speaking the diets were not badly defective in Vitamin $B_1$, but nearly half the women were not obtaining as high an intake as was really desirable. Vitamin C shortage also affected about half the women, but once again the deficiency was not nearly so great as had been expected. The general impression was that the women were on the average better nourished than had been expected from previous surveys of comparable groups of the ordinary population. Many of the women were clearly following advice given at the antenatal centres, and fresh fruit and eggs frequently entered into their daily diet. The same was true of milk. The women said they were taking these foods especially because they had been advised that the health of their babies would thereby be improved. There were, however, instances in which the dietaries were grossly defective.

The committee next decided on the amounts of vitamins and minerals required to make up the deficiencies noted. The daily supplements used for the experiment were:

Saccharated iron carbonate, gr. 18 (1.2 g.), equivalent to 0.26 g. ferrous iron.

Calcium lactate, gr. 30 (2 g.) equivalent to 0.26 g. calcium.

Minute quantities of iodine, manganese and copper. Adsorbate of vitamin $B_1$ containing all factors of the B complex ($B_1$ content standardized at 200 I.U. per g.) gr. 15 (1 g.).

Vitamin C (ascorbic acid), 100 mg.

Halibut liver oil (vitamin A, 52,000 I.U. per g. and vitamin D 2,500 I.U. per g.), min. 6 (0.36 g.).

It was decided that the investigation should include a minimum of 5,000 pregnant women to be enrolled at the antenatal clinics of the participating hospitals. All women attending at the clinics from the date of the commencement of the research were included with the exception of two groups. (*a*) Those whose pregnancy had advanced beyond the 24th week. This meant that in all cases there was an interval of 16 or more weeks between the commencement of the research and the date of delivery. (*b*) Women who suffered from any disease or physical abnormality.

In all 5,644 pregnant women were initially enrolled but of these only 5,022 remained in the investigation. The rejections were as follows:

| | |
|---|---|
| (1) Withdrawals on account of war made up chiefly of women who were evacuated from the London area ... ... ... ... ... | 494 |
| (2) Women who had twin births ... | 39 |
| (3) Women who miscarried at an early stage ... ... ... ... | 89 |
| Total | 622 |

In each hospital the women at the time of enrolment were divided into two main groups by placing them alternately on separate lists. In this way we attempted to equate the numbers and the age distribution. The women in one group received the supplements (treated), while those in the other served as controls (controls). Within each of these groups the women were further classified into (1) women pregnant for the first time and (2) women with a history of one or more previous pregnancies. Again each of these two groups were subdivided according to age: (*a*) women under 25; (*b*) women between 25 and 30 years; and (*c*) women over 30 years.

The extent to which we were successful in our sub-division is shown in Table I.

The slight divergence that has occurred is due to the slightly different numbers in the respective groups of the cases eliminated from the investigation for the reasons given above. The age distribution amongst the various groups is shown in Table I. It will be noted that the primiparae were mainly under age 30 (80 per cent), whilst the multiparae were equally distributed above and below this age. The total women available for the investigation were distributed as follows:

| | Treated | Controls | Total |
|---|---|---|---|
| Primiparae ... | 1530 | 1513 | 3043 |
| Multiparae ... | 980 | 999 | 1979 |
| | 2510 | 2512 | 5022 |

TABLE I.
*Distribution by Age and Parity.*

| Age group | Primiparae | | | | Multiparae | | | |
|---|---|---|---|---|---|---|---|---|
| | Treated | | Controls | | Treated | | Controls | |
| | No. | per cent | No. | per cent | No. | per cent | No. | per cent |
| 15– | 90 | 5.9 | 84 | 5.6 | 8 | 0.9 | 9 | 0.9 |
| 20– | 514 | 33.6 | 527 | 34.8 | 142 | 14.5 | 168 | 16.8 |
| 25– | 633 | 41.4 | 623 | 41.2 | 371 | 37.9 | 349 | 34.9 |
| 30– | 226 | 14.8 | 220 | 14.5 | 282 | 28.8 | 286 | 28.6 |
| 35– | 63 | 4.1 | 54 | 3.6 | 139 | 14.2 | 151 | 15.1 |
| 40– | 4 | 0.3 | 5 | 0.3 | 38 | 3.9 | 36 | 3.6 |
| All ages | 1530 | 100 | 1513 | 100 | 980 | 100 | 999 | 100 |

## THE MOTHER.

### TOXAEMIA.

At the start of the research it was decided to regard as toxaemia (*a*) cases which exhibited hypertension—a systolic blood-pressure of or above 140 mm. Hg. or a diastolic pressure of or above 90 mm. Hg. —with or without albuminuria, and (*b*) cases in which there was no hypertension and in which the diagnosis was based upon albuminuria.

*Toxaemia According to Revised Standard.*

Within recent years, and increasingly since the date at which this investigation was planned and the standard as given above was laid down, it has come to be recognized that a diagnosis of toxaemia cannot be based upon hypertension by itself, as this frequently connotes not a true or specific pregnancy toxaemia but an essential hypertension. The exclusion from the above groups of cases with hypertension as the sole clinical condition leaves those women in whom the diagnosis of toxaemia is based upon albuminuria, oedema, etc., with or without, but generally with, hypertension. This treatment of the figures may result in the exclusion of some cases in which the hypertensive state is due to toxaemia, but any such disadvantage is offset by the fact that, apart from any possible differential benefit derived from the supplementary diet in one group, each group is being similarly treated. It has the advantage of segregating for special study those cases in which the diagnosis of toxaemia rests on a reasonably secure foundation.

On this basis the primigravidae who received the additional dietary ingredients had an incidence of toxaemia of 5.4 per cent, while in the primigravidae who did

not receive any additional diet the percentage was 7.4. The difference and its standard error was 2±0.9, which means that the odds are nearly 40 to 1 against such a result being obtained by mere chance. The figures were also favourable to the parous women, but not to a significant degree, the percentages being 3.6 and 5.2 respectively, the difference being 1.6±0.9 (see Table II). These results are striking, and indicate that the women receiving the special diet are protected against the risk of toxaemia in a ratio which is almost 30 per cent. When it is remembered that, next to puerperal sepsis, toxaemia is the most important cause of the maternal death-rate (about 20 per cent of the total)* in addition to being one of the most fertile sources of chronic ill-health after childbirth, the findings of the committee assume a significance which it is hardly possible to over estimate. This investigation has been carried out in the London area, in which it is known that the incidence of toxaemia is low.

In a further classification based upon the criteria generally accepted for "pre-eclampsia"—namely, hypertension with albuminuria, oedema, et cetera—the following toxaemia rates were obtained: treated primigravidae, 4.51 per cent; untreated primigravidae, 6.42 per cent; the difference being 1.91±0.82; treated multiparae, 3.16 per cent; untreated multiparae, 4.6 per cent; the difference being 1.44±0.87 (see Table II).

TABLE II.
*Pregnancy Toxaemia.*

| | No. of women | Hypertension only | | Albuminuria with or without hypertension | | Hypertension with albuminuria, etc. (pre-eclampsia) | |
|---|---|---|---|---|---|---|---|
| | | Cases | Per cent | Cases | Per cent | Cases | Per cent |
| *Primiparae*: | | | | | | | |
| Treated ... ... | 1530 | 332 | 21.7 | 83 | 5.4 | 69 | 4.51 |
| Controls ... ... | 1512 | 368 | 24.3 | 112 | 7.4 | 97 | 6.42 |
| Difference (C–T) | | 2.6±1.5 | | 2.0±0.9 | | 1.91±0.82 | |
| *Multiparae*: | | | | | | | |
| Treated ... ... | 980 | 179 | 18.3 | 35 | 3.6 | 31 | 3.16 |
| Controls ... ... | 999 | 166 | 16.6 | 52 | 5.2 | 46 | 4.60 |
| Difference (C–T) | | −1.7±1.7 | | 1.6±0.9 | | 1.44±0.87 | |
| Total ... ... | 5021 | 1045 | | 282 | | 243 | |

*Differences According to Hospital.*

There are marked differences in the incidence of albuminuric toxaemia in individual hospitals. Thus in Hospital B in 234 primiparae the rate was 2.1 per cent and in 232 multiparae 2.1 per cent. At the upper extreme Hospital F had a rate of 8.7 per cent in 287 primiparae and of 11.4 per cent in 228 multigravidae.

*Toxaemia According to Original Standard.*

Table III represents the data based upon this standard and it shows the vital importance of age and parity. The rates are seen to be correlated in a positive manner with each of these factors (see Table III).

* Since the years when this investigation was carried out and owing chiefly to the fall in the death-rate from puerperal sepsis the comparative importance of toxaemia has increased. This condition is now responsible for just under 30 per cent of the total maternal mortality.

*Age and Parity.*

*Primiparae.* It will be seen that for the "All Ages" group the percentage of toxaemia in the treated primiparae is significantly lower than in the controls, the respective figures being 27.1 per cent and 31.7 per cent, a difference of 4.6±1.7 per cent. This result, however, is due to the dominating influence of the statistical experience of women aged 25 to 30, where the difference is 7.7±2.6 per cent. At the younger and older ages the difference, although still favouring the treated groups, is statistically unimportant.

*Multiparae.* In the "All Ages" group the treated incidence of 21.8 per cent which equalled that for the controls, and, in 2 out of 3 specific age groups, they were, if anything at a disadvantage.

*Duration of Treatment.*

If the treatment were effective in controlling incidence one might expect an inverse relationship between the duration of the treatment and the morbidity-rate. The results are given in Table IV and they do not support this hypothesis. In point of fact they suggest the existence of a saturation level with 16 to 20 weeks treatment at which the best results are obtained. Here the treated primiparae are statistically superior to the controls—20.7 per cent as against 31.7 per cent. The multiparae are not quite so definite—18.6 per cent against 21.8 per cent. With prolongation of treatment beyond this interval the incidence increases and, for a duration of 24 weeks or more, the experience of the treated is worse than that for the controls. It is possible that, since no allowance was made for age in the compilation of this table, some of the difference observed may be due to this cause, but, superficially, there seems no reason to suppose that there was any correlation between age and length of treatment (see Table IV).

TABLE III.
*Pregnancy Toxaemia (Original Standard)*
*Distribution by Age and Parity.*

| | Primiparae | | | | | | |
|---|---|---|---|---|---|---|---|
| | Treated | | | Controls | | | Difference |
| Age group | No. of observations | No. toxaemic | Per cent | No. of observations | No. toxaemic | Per cent | (C–T) |
| Under 25 | 604 | 144 | 23.8 | 610 | 166 | 27.2 | 3.4±2.5 |
| 25–29 | 633 | 166 | 26.2 | 623 | 211 | 33.9 | 7.7±2.6 |
| 30 and over | 293 | 105 | 35.8 | 279 | 102 | 36.6 | 0.8±4.0 |
| All ages | 1530 | 415 | 27.1 | 1512 | 479 | 31.7 | 4.6±1.7 |
| | Multiparae | | | | | | |
| | Treated | | | Controls | | | Difference |
| Age group | No. of observations | No. toxaemic | Per cent | No. of observations | No. toxaemic | Per cent | (C–T) |
| Under 25 | 150 | 27 | 18.0 | 177 | 26 | 14.7 | −3.3±4.1 |
| 25–29 | 371 | 69 | 18.6 | 349 | 71 | 20.4 | 1.8±2.9 |
| 30 and over | 459 | 118 | 25.7 | 473 | 121 | 25.6 | −0.1±2.9 |
| All ages | 980 | 214 | 21.8 | 999 | 218 | 21.8 | 0.0±1.9 |

*Differences in Incidence of Toxaemia According to Hospital.*

A great range in the incidence of toxaemia, according to the above standards, was found to obtain in the different hospitals. Thus, in primiparae this incidence varied from 58.9 per cent in Hospital F to 5.6 per cent in Hospital B. The corresponding incidences in the multiparae were 40.3 and 6 per cent. In Table V the figures for the hospitals are shown. It is difficult to explain the extreme variations. The results for the multiparae reveal no such correlation. There is no satisfactory evidence in favour of treatment. In regard to the primiparae the rates for the treated are 4.6 per cent and for the controls 4.2 per cent with an insignificant difference of $-0.4 \pm 0.7$ in favour of the latter. The comparable values for the multiparae were 2.3 per cent and 2.2 per cent.

*Seasonal Influence* (Table VII). There is a well-defined seasonal trend in the prevalence of sepsis amongst primi-

TABLE IV.
*Pregnancy Toxaemia (Original Standard)*
*Distribution by Duration of Treatment.*

| | Primiparae | | | | Multiparae | | | |
|---|---|---|---|---|---|---|---|---|
| Length of treatment | No. of observations | No. toxaemic | Per cent | Difference (C–T) | No. of observations | No. toxaemic | Per cent | Difference (C–T) |
| Controls | 1512 | 479 | 31.7 | | 999 | 218 | 21.8 | |
| Under 16 weeks | 288 | 72 | 25.0 | $6.7 \pm 3.0$ | 171 | 35 | 20.5 | $1.3 \pm 3.4$ |
| 16– | 411 | 85 | 20.7 | $11.0 \pm 2.5$ | 279 | 52 | 18.6 | $3.2 \pm 2.8$ |
| 20– | 414 | 114 | 27.5 | $4.2 \pm 2.6$ | 274 | 67 | 24.5 | $-2.7 \pm 2.8$ |
| 24 or more | 417 | 144 | 34.5 | $-2.8 \pm 2.6$ | 256 | 60 | 23.4 | $1.6 \pm 2.9$ |

That they cannot be attributed to differences in ages in the different populations is clearly shown by a reference to column 1, which expresses under primiparae the percentage of women under age 25 and under multigravidae the percentage under age 30 (see Table V).

SEPSIS.

The results (Table VI) conform to the usual clinical experience that the incidence of sepsis is related to parity. The rate amongst the primiparae is approximately 4.5 per cent as compared with 2.2 per cent amongst the multiparae, an excess of about 100 per cent (see Table VI).

*Influence of Age and Parity.* It is seen that the incidence increases with age for primiparae, the rates being 3.3 per cent for age under 25, 5 per cent for age 25 to 30 and nearly 6 per cent for women over 30. parae, the percentage during October–March being 5.3 as compared with 3.5 during April–September. On the other hand, it is only amongst the controls for multiparae that the seasonal factor is demonstrated, the respective winter and summer rates being 2.8 per cent and 1.5 per cent, but at no period of the year, either for primiparae or multiparae are the sepsis rates of the treated statistically better than those of the controls (see Table VII).

*Influence of Duration of Treatment.* (Table VIII). When the data were classified according to duration of treatment and the results compared with those for the controls, no apparent divergence was noted. The primiparae who had taken the vitamin diet for 24 weeks and more had a sepsis-rate of 4.8 per cent as against 4.2

per cent for the controls. The comparable figures for the multiparae were 2.2 per cent and 2.3 per cent in both instances, negligible differences. Furthermore the results reveal no negative relationship between the incidence and the length of time over which treatment was taken as the rates amongst women who had the diet for longer than 6 months are no better than those listed for a duration of less than 4 months (see Table VIII).

*Distribution by Site.* Table IX exhibits the various types of sepsis met with (see Table IX).

### Duration of Labour.

The data under this heading are shown in Table X, and it is seen that at "all ages" there is no significant difference between the treated and controls. In the individual age groups the only difference is in the primiparae class 30 and over, a difference of 3.3 hours in favour of the treated which almost approaches significance. In the other age groups, both for primiparae and multiparae there is no significant difference between the treated and controls.

The table demonstrates in a very clear form the high positive correlation between

Table V.

*Incidence of Toxaemia According to Hospitals.*
(Original Standard)

Primiparae

| Percentage under age 25 | Hospital | Total numbers | Toxaemia per cent | |
|---|---|---|---|---|
| | | | Albuminuria with or without hypertension | Hypertension |
| 60–70 | B | 234 | 2.1 | 5.6 |
| 50–60 | F | 287 | 11.5 | 58.9 |
| 40–50 | A | 354 | 9.0 | 31.6 |
| | E | 55 | 10.9 | 58.2 |
| 30–40 | C | 505 | 9.7 | 27.8 |
| | D | 305 | 6.2 | 28.9 |
| | G | 263 | 4.9 | 24.3 |
| | H | 451 | 5.1 | 24.6 |
| 20–30 | I | 303 | 4.3 | 28.4 |
| | J | 286 | 5.2 | 27.6 |

Multiparae

| Percentage under age 30 | Hospital | Total numbers | Toxaemia per cent | |
|---|---|---|---|---|
| | | | Albuminuria with or without hypertension | Hypertension |
| 70–80 | E | 57 | 3.5 | 36.8 |
| 60–70 | A | 239 | 5.9 | 27.6 |
| 50–60 | B | 232 | 2.2 | 6.0 |
| | C | 253 | 5.1 | 18.6 |
| | D | 71 | 5.6 | 32.4 |
| | H | 148 | 1.4 | 20.2 |
| | I | 223 | 1.8 | 22.4 |
| 40–50 | F | 228 | 11.8 | 40.3 |
| | G | 218 | 2.3 | 18.3 |
| | J | 310 | 2.9 | 15.8 |

TABLE VI.
*Sepsis.*
*Distribution by Age and Parity.*

Primiparae.

| Age group | Treated: No. of observations | Treated: Sepsis | Treated: Per cent | Controls: No. of observations | Controls: Sepsis | Controls: Per cent | Difference (C–T) |
|---|---|---|---|---|---|---|---|
| Under 25 | 604 | 20 | 3.3 | 609 | 21 | 3.4 | 0.1 ± 1.0 |
| 25–29 | 631 | 34 | 5.4 | 623 | 28 | 4.5 | −0.9 ± 1.2 |
| 30 and over | 293 | 17 | 5.8 | 277 | 15 | 5.4 | −0.4 ± 1.9 |
| All ages | 1528 | 71 | 4.6 | 1509 | 64 | 4.2 | −0.4 ± 0.7 |

Multiparae

| Age group | Treated: No. of observations | Treated: Sepsis | Treated: Per cent | Controls: No. of observations | Controls: Sepsis | Controls: Per cent | Difference (C–T) |
|---|---|---|---|---|---|---|---|
| Under 25 | 150 | 4 | 2.7 | 177 | 2 | 1.1 | −1.6 ± 1.5 |
| 25–29 | 371 | 10 | 2.7 | 349 | 11 | 3.2 | 0.5 ± 1.3 |
| 30 and over | 458 | 9 | 2.0 | 470 | 9 | 1.9 | −0.1 ± 0.9 |
| All ages | 979 | 23 | 2.3 | 996 | 22 | 2.2 | −0.1 ± 0.7 |

TABLE VII.
*Sepsis.*
*Distribution by Season of Confinement*

Primiparae

| Period | Treated: No. of observations | Treated: Sepsis | Treated: Per cent | Controls: No. of observations | Controls: Sepsis | Controls: Per cent | Difference (C–T) |
|---|---|---|---|---|---|---|---|
| January–March | 416 | 21 | 5.0 | 391 | 17 | 4.3 | −0.7 ± 1.5 |
| April–June | 369 | 12 | 3.3 | 367 | 12 | 3.3 | 0.0 ± 1.3 |
| July–September | 334 | 13 | 3.9 | 384 | 14 | 3.6 | −0.3 ± 1.4 |
| October–December | 409 | 25 | 6.1 | 367 | 21 | 5.7 | −0.4 ± 1.7 |
| All periods | 1528 | 71 | 4.6 | 1509 | 64 | 4.2 | −0.4 ± 0.7 |

Multiparae

| Period | Treated: No. of observations | Treated: Sepsis | Treated: Per cent | Controls: No. of observations | Controls: Sepsis | Controls: Per cent | Difference (C–T) |
|---|---|---|---|---|---|---|---|
| January–March | 263 | 5 | 1.9 | 274 | 9 | 3.3 | 1.4 ± 1.4 |
| April–June | 206 | 2 | 1.0 | 223 | 5 | 2.2 | 1.2 ± 1.2 |
| July–September | 235 | 8 | 3.4 | 243 | 2 | 0.8 | −2.6 ± 1.3 |
| October–December | 275 | 8 | 2.9 | 256 | 6 | 2.3 | −0.6 ± 1.4 |
| All periods | 979 | 23 | 2.3 | 996 | 22 | 2.2 | −0.1 ± 0.7 |

age and duration of labour known to exist in primiparae. The figures rise progressively from 18 hours in the age period 15 to 20 to about 26 hours at 30 and over. There is no age correlation in multiparae which throughout the various age groups varies little from a mean of about 12 hours; i.e., about half that for primiparae (see Table X).

## THE INFANT.

### LENGTH OF GESTATION.

The length of pregnancies is analysed (Table XI) under 40 weeks, 40 weeks exactly, and over 40 weeks. It is seen that the two distributions (Treated and Control) differ significantly. The value of X2 was 11.186 with $P<0.01$. This result means that the

TABLE VIII.
*Sepsis.*
*Distribution by Duration of Treatment.*

Primiparae

| Length of Treatment | No. of observations | Number of cases of sepsis | Per cent | Difference (control–treated) |
|---|---|---|---|---|
| Controls ... ... ... | 1509 | 64 | 4.2 | |
| Under 16 weeks ... ... | 288 | 11 | 3.8 | $0.4 \pm 1.3$ |
| 16– ... ... ... | 411 | 24 | 5.8 | $-1.6 \pm 1.2$ |
| 20– ... ... ... | 412 | 16 | 3.9 | $0.3 \pm 1.1$ |
| 24 weeks and more ... | 417 | 20 | 4.8 | $-0.6 \pm 1.1$ |

Multiparae

| Length of Treatment | No. of observations | Number of cases of sepsis | Per cent | Difference (control–treated) |
|---|---|---|---|---|
| Controls ... ... ... | 996 | 22 | 2.2 | |
| Under 16 weeks ... ... | 171 | 4 | 2.3 | $-0.1 \pm 1.2$ |
| 16– ... ... ... | 278 | 8 | 2.9 | $0.7 \pm 1.0$ |
| 20– ... ... ... | 274 | 5 | 1.8 | $0.4 \pm 1.0$ |
| 24 weeks and more ... | 256 | 6 | 2.3 | $-0.1 \pm 1.0$ |

TABLE IX.
*Distribution by Site.*

| | Primiparae | | Multiparae | |
|---|---|---|---|---|
| | Treated | Control | Treated | Control |
| 1. General septicaemia ... ... ... ... | 1 | | | |
| 2. Local pelvic sepsis ... ... ... ... | 21 | 23 | 9 | 9 |
| 3. Mastitis ... ... ... ... ... ... | 13 | 13 | 6 | 7 |
| 4. Urinary tract infection ... ... ... | 28 | 18 | 6 | 5 |
| 5. Sepsis after Caesarean section ... ... | 5 | 3 | 2 | 1 |
| 2 and 4 ... ... ... ... ... ... | 1 | 2 | | |
| 3 and 4 ... ... ... ... ... ... | 1 | 1 | | |
| 2 and 3 ... ... ... ... ... ... | | 1 | | |
| 4 and 5 ... ... ... ... ... ... | | 2 | | |
| 1 and 2 and 4 ... ... ... ... ... | | 1 | | |
| Local sepsis ... ... ... ... ... | 1 | | | |
| All sepsis ... ... ... ... ... ... | 71 | 64 | 23 | 22 |

probability of obtaining a similar distribution by chance is less than one in 100 trials. This result—the smaller incidence of prematurity among the treated women so is a decreasing function of age (Table XII). Of the primiparous women aged under 25 years, 90 per cent breast feed their babies and for mothers aged 30 the propor-

TABLE X.
*Duration of Labour in Hours.*

| | Primiparae | | | | | |
|---|---|---|---|---|---|---|
| | 15–19 | | 20–24 | | 25–29 | |
| Age group | No. of observations | Mean and S.E. | No. of observations | Mean and S.E. | No. of observations | Mean and S.E. |
| Treated | 90 | 17.5±1.40 | 511 | 21.5±0.81 | 619 | 23.2±0.72 |
| Controls | 84 | 18.3±1.25 | 523 | 20.5±0.73 | 616 | 22.6±0.73 |
| Difference (C–T) | | 0.8±1.9 | | −1.0±1.1 | | −0.6±1.0 |

| | 30 and over | | All ages | |
|---|---|---|---|---|
| Age group | No. of observations | Mean and S.E. | No. of observations | Mean and S.E. |
| Treated | 283 | 27.3±1.38 | 1503 | 23.1±0.49 |
| Controls | 272 | 24.0±1.35 | 1495 | 21.9±0.47 |
| Difference (C–T) | | −3.3±1.9 | | −1.2±0.7 |

| | Multiparae | | | | | |
|---|---|---|---|---|---|---|
| | Under 25 | | 25–29 | | 30–34 | |
| Age group | No. of observations | Mean and S.E. | No. of observations | Mean and S.E. | No. of observations | Mean and S.E. |
| Treated | 149 | 11.2±0.78 | 366 | 12.2±0.56 | 278 | 10.8±0.59 |
| Controls | 177 | 11.1±0.72 | 346 | 12.4±0.65 | 281 | 12.5±0.76 |
| Difference (C–T) | | −0.1±1.1 | | 0.2±0.9 | | 1.7±1.0 |

| | 35 and over | | All ages | |
|---|---|---|---|---|
| Age group | No. of observations | Mean and S.E. | No. of observations | Mean and S.E. |
| Treated | 173 | 11.9±0.92 | 966 | 11.6±0.34 |
| Controls | 182 | 11.3±0.72 | 986 | 12.0±0.37 |
| Difference (C–T) | | −0.62±1.2 | | 0.4±0.5 |

—is of special importance in view of the fact that about 50 per cent of infant deaths under one month are due to prematurity (see Tables X and XI).

### BREAST FEEDING.

The ability of the mother to breast feed her baby, or, rather, the proportion who do tion is 76 per cent. For the youngest primiparae the controls have a statistically better record than the treated, the respective rates being 91 per cent and 87.3 per cent, or a difference of 3.7±1.8, which is just outside the limits of random error due to sampling. For women of other ages the results are absolutely identical.

Amongst multiparae there is an inverse correlation with age as amongst the primiparae. If we take the age group 30 and over as one in which malnutrition is most likely to occur because of the existence of a larger household we find that the controls have a better record than the treated; 89.4 per cent of the former breast fed their children as compared with 85.3 per cent of the latter, a difference of $4.1 \pm 2.2$, which approaches the level of significance.

The influence of duration of treatment was studied. It was found that, although the percentage of children breast fed increased with extended treatment, it is only when the mothers had taken the supple-

TABLE XI.

*Period of Gestation and Length of Treatment.*

| | Primiparae | | | | Multiparae | | | |
|---|---|---|---|---|---|---|---|---|
| | Treated | | Controls | | Treated | | Controls | |
| | No. | Per cent | No. | Per cent | No. | Per cent | No. | Per cent |
| Under 40 weeks | 308 | 20.1 | 362 | 23.9 | 197 | 20.1 | 241 | 24.2 |
| 40 weeks exactly | 1060 | 69.3 | 990 | 65.5 | 674 | 68.8 | 654 | 65.7 |
| More than 40 weeks | 161 | 10.5 | 160 | 10.6 | 109 | 11.1 | 101 | 10.1 |
| Not stated | 1 | | 1 | | | | 3 | |
| Total | 1529 | 100 | 1512 | 100 | 980 | 100 | 996 | 100 |
| | 1530 | | 1513 | | 980 | | 999 | |

TABLE XII.

*Breast feeding.*
*Distribution by Age of Mother and Parity.*

| | Primiparae | | | | | | |
|---|---|---|---|---|---|---|---|
| | Treated | | | Controls | | | Difference |
| | No. of live births | No. breast fed | Per cent | No. of live births | No. breast fed | Per cent | (controls–treated) |
| Under 25 | 588 | 513 | 87.3 | 590 | 537 | 91.0 | $3.7 \pm 1.8$ |
| 25–29 | 615 | 515 | 83.7 | 606 | 507 | 83.7 | $0 \pm 2.1$ |
| 30 and over | 284 | 218 | 76.8 | 267 | 205 | 76.8 | $0 \pm 3.6$ |
| All ages | 1487 | 1246 | 83.8 | 1463 | 1249 | 85.4 | $1.6 \pm 1.3$ |
| | Multiparae | | | | | | |
| | Treated | | | Controls | | | Difference |
| | No. of live births | No. breast fed | Per cent | No. of live births | No. breast fed | Per cent | (controls–treated) |
| Under 25 | 147 | 133 | 90.5 | 176 | 151 | 85.8 | $-4.7 \pm 3.7$ |
| 25–29 | 367 | 332 | 90.5 | 342 | 311 | 90.9 | $0.4 \pm 2.2$ |
| 30 and over | 442 | 377 | 85.3 | 454 | 406 | 89.4 | $4.1 \pm 2.2$ |
| All ages | 956 | 842 | 88.1 | 972 | 868 | 89.3 | $1.2 \pm 1.4$ |

mentary diet for 24 weeks and over that their ability to breast feed was slightly better than that of the controls. The respective values were 87.4 per cent as against 85.4 per cent, with a difference of $-2 \pm 2$ which is within the range of a chance variation.

There is a wide range in the percentage of breast feeding in individual hospitals. Thus, whilst in hospital G the rate is 68.8 per cent, in hospitals B and J the rates are 92.9 and 94.3 per cent respectively. The values in the multiparae class are, on the average, higher than those in the primiparae. These results suggest that the incidence of breast feeding is to a large extent determined by such factors as hospital practice and discipline and that it does not necessarily reflect the physiological ability of the mother to feed her baby.

### Infant Mortality.

It might be expected that, as the babies of the treated mothers had the more favourable experience in regard to prematurity and birth weight, they would show lower rates in respect of stillbirth and neonatal mortality. In regard to stillbirth this was found to be the case as is shown by the following table (see Table XIII).

Table XIII.
*Infant Mortality.*

| Primiparae | Treated | Per cent | Controls | Per cent |
|---|---|---|---|---|
| Stillbirths ... ... ... | 37 | 2.4 | 47 | 3.1 |
| Died before 8 days ... ... | 20 | 1.3 | 12 | 0.8 |
| Total ... ... ... ... | 57 | 3.7 | 59 | 3.9 |

| Multiparae | Treated | Per cent | Controls | Per cent |
|---|---|---|---|---|
| Stillbirths ... ... ... | 20 | 2.0 | 22 | 2.2 |
| Died before 8 days ... ... | 14 | 1.4 | 12 | 1.2 |
| Total ... ... ... ... | 34 | 3.4 | 34 | 3.4 |

It is shown, however, that this advantage does not apply in regard to neonatal mortality which is appreciably higher in babies born to treated primiparae and slightly higher in treated multiparae.

### References.

1. *Brit. Med. Journ.*, 1942, ii, 77.
2. *Lancet*, 1942, ii, 10.

# Sensitization of the Vascular System in Pre-eclamptic Toxaemia and Eclampsia

BY

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HYPERTENSION is one of the earliest and most constant signs of pre-eclamptic toxaemia, yet its cause remains undetermined. The investigations of Kellar and Sutherland[1] have shown that it is due not to a nervous mechanism but to a humoral substance. It is not known what this humoral substance is, but it has been demonstrated that it is not renin, hypertensin,[2] adrenalin or tyramin.[3] Hoffman, Anselmino and Kennedy[4] claimed that in pre-eclamptic toxaemia and eclampsia there was in the patient's circulation excess of a pressor substance derived from the posterior pituitary gland. This pressor principle was demonstrable in excess in ultra-filtrates of the plasma of all pre-eclamptic or eclamptic patients whose blood-pressure exceeded 180 mm. Hg. Other workers, however, failed to confirm these claims.[5, 6, 7, 8, 9, 10] Byrom,[11, 12] discussing the question as to whether excess of a pressor substance can be the cause of the hypertension, says that the amount of vasopressin required to produce it would be so large that "it is difficult to believe that eclampsia can be due wholly to over secretion of this hormone. The question therefore arises whether some dislocation of equilibrium arising out of pregnancy may not render the vessels over sensitive to this hormone." Bourne and Burn[13] had found that the response of uterine muscle to oxytocin could be greatly enhanced by oestrin (oestradiol benzoate). This suggested to Byrom the study of the effect of sex hormones on the response of the rat to vasopressin. By injecting measured amounts of vasopressin he produced lesions closely resembling those of eclampsia, including a rise of blood-pressure of 50 mm. Hg. or more, anaemic infarcts in the kidneys symmetrically distributed throughout the deeper layers of the cortex, focal necrosis in the liver, albuminuria, coma and death. He believed the visceral lesions to be due to arteriolar spasm. He also found that the sensitivity of the rat could be so increased by preliminary treatment with oestrogens, that the same effect could be produced by one tenth of the original dose of vasopressin, and that in unspayed rats the sensitization could equally well be caused by gonadotropic hormone (aqueous solution of extract of pregnancy urine). The sensitization was not prevented or modified by simultaneous injection of progesterone. Byrom concluded that gonadotropic hormone, though predominantly luteinizing in action, caused sensitization by stimulating ovarian secretion of oestrin and that oestrin-sensitization is in some way concerned in the genesis of eclampsia.

Shockaert and Lambillon[14] using tonephin, and simultaneously and independently Dieckmann and Michel[15] using pituitrin, showed that nulliparous women, normal pregnant women and women suffering from pre-eclamptic toxaemia reacted differently to injected pressor substances. This work was confirmed in its essentials by de Valera and Kellar[16] and Browne.[17] The

results of these different workers are shown in the following table (Table I).

It will be seen that while the results differ in certain details all agree that in pre-eclamptic toxaemia there is, as compared with normal pregnancy at or near term, a very severe reaction indicated by a large rise of systolic pressure after injection of a standard amount of the pressor substance. This difference in reaction must be due to a difference in sensitivity of the vascular system in the one as compared with the other.

TABLE I.

*Reactions to Pressor Substances (Rise of Systolic Arterial Pressure in mm. Hg. in Normal and Toxaemic Women).*
(Comparative Results of Various Workers.)

| | Shockaert and Lambillon (Tonephin) | Dieckmann and Michel (Pituitrin) | de Valera and Keller (Tonephin) | Browne (Tonephin) |
|---|---|---|---|---|
| Normal women not pregnant ... ... | 45 | — | 35 | 21.3 |
| Normal pregnant women ... ... ... | 13 | 11 | 23 | 33.2 |
| Pre-eclamptic toxaemia ... ... ... | 55 | 51 | 43 | 54 |
| Pregnancy with chronic hypertension | 16 | 7.7 | — | 53 |
| Normal puerperal ... ... ... ... | 44 | — | 44 | 48.2 |

THE PRESENT INVESTIGATION.

Two questions now arise: (1) Is this abnormal sensitivity constitutional or is it acquired in the course of the development of the pre-eclamptic toxaemia? (2) If it is acquired what causes it?

It seemed that the first question could be answered by testing the reactions to pressor substances in a series of normal women in the early weeks of pregnancy and comparing the results with those obtained in any patients of the group who later developed pre-eclamptic toxaemia. This was done in 27 women at their first attendance at the antenatal clinic. The duration of the pregnancy at this time varied from 8 to 20 weeks and the average was 13 weeks counting from the first day of the last menstrual period. The results are shown in Table II. In carrying out these tests the base level of the blood-pressure is first obtained by making successive blood-pressure estimations with the patient at rest, lying down. This generally entails 7 or 8 tests spread over half an hour or more. The lowest systolic reading and the lowest diastolic reading are taken as the "base level." Tonephin 0.66 c.cm. is then injected into an arm, care being taken to inject slowly and to deflate the cuff as soon as the needle has entered the vein. Systolic readings are then taken as rapidly and in as quick succession as possible for 2 or more minutes. The difference between the systolic basic pressure and the highest systolic reading after injection is a measure of the reaction to the tonephin. Diastolic readings may also be made but in the writer's experience they are liable to be inaccurate, and in attempting to note them so much time is wasted that the highest level reached by the systolic pressure is apt to be missed. This only refers to estimations of the diastolic pressure after injection of tonephin. In obtaining the basic level before tonephin is injected it is easy to obtain the diastolic pressure. Those given in Table II are the points at which the sound disappeared.

TABLE II.

*Reactions to Pressor Substance in Early Normal Pregnancy.*

| Identification number | Weeks pregnant | Base level of blood-pressure (mm. Hg.) | | Systolic blood-pressure after tonephin (mm. Hg.) | Difference in systolic pressure (mm. Hg.) | Signs of toxaemia in late pregnancy if blood-pressure over 120/80 |
|---|---|---|---|---|---|---|
| | | Systolic | Diastolic | | | |
| 1 | 13 | 118 | 70 | 148 | 30 | 135/80 |
| 2 | 20 | 112 | 46 | 130 | 18 | None |
| 3 | 11 | 114 | 55 | 142 | 28 | 132/82 |
| 4 | 11 | 140 | 65 | 180 | 40 | 134/80 |
| 5 | 20 | 118 | 58 | 144 | 26 | 141/80 |
| 6 | 13 | 115 | 50 | 135 | 20 | None |
| 7 | 17 | 134 | 55 | 150 | 16 | 150/95 |
| 8 | 10 | 110 | 50 | 145 | 35 | 124/84 |
| 9 | 13 | 118 | 60 | 132 | 14 | None |
| 10 | 11 | 118 | 40 | 140 | 22 | 150/100 |
| 11 | 10 | 102 | 50 | 126 | 24 | None |
| 12 | 14 | 120 | 45 | 146 | 26 | 130/86 |
| 13 | 20 | 116 | 55 | 130 | 14 | None |
| 14 | 11 | 120 | 50 | 125 | 5 | 150/100 |
| 15 | 16 | 110 | 50 | 124 | 14 | 122/80 |
| 16 | 13 | 100 | 50 | 105 | 5 | None |
| 17 | 14 | 120 | 50 | 140 | 20 | None |
| 18 | 11 | 110 | 60 | 130 | 20 | None |
| 19 | 10 | 106 | 40 | 128 | 22 | Evacuated |
| 20 | 9 | 90 | 40 | 92 | 2 | Evacuated |
| 21 | 10 | 108 | 50 | 150 | 42 | I U death at 20 weeks |
| 22 | 8 | 102 | 45 | 130 | 28 | Evacuated |
| 23 | 16 | 100 | 45 | 130 | 30 | Evacuated |
| 24 | 10 | 112 | 18 | 140 | 28 | Evacuated |
| 25 | 17 | 98 | 45 | 125 | 27 | Illegitimate pregnancy. Miscarriage after 21 weeks |
| 26 | 12 | 126 | 55 | 130 | 4 | Evacuated |
| 27 | 12 | 110 | 40 | 120 | 10 | Evacuated |

It was expected that some of these 27 women would develop pre-eclamptic toxaemia. The reaction to tonephin of any who did so could then again be tested. If it were found to be significantly raised it would show that the sensitization which must necessarily account for the heightened reaction was acquired in the course of the pregnancy in the period between the first and second tests. It was decided to adopt for the purpose of this investigation a blood-pressure of 140/90 or over with or without oedema and albuminuria as the standard of pre-eclamptic toxaemia. Seven of the women were evacuated to the country during the air attacks on London and in 2 others the pregnancy ended prematurely. Three of the remaining women actually reached the standard mentioned, viz., Numbers 7, 10 and 14 in Table II. In Number 14 difficulty was met with in entering the vein at the second test which had in consequence to be abandoned. The essential details regarding the remaining 2, are as follows:

NUMBER 7. Primigravida, aged 21, L.M.P. January 7th to 12th, 1944. First attendance on May 8th, that is, 17th week of pregnancy.

Apparently healthy; urine normal; blood-pressure 140/62; base level 100/40. After injection of tonephin systolic pressure rose to 150 mm. Hg. Reaction 16 mm. Hg. On September 11th, 1944, her blood-pressure was 150/95. Slight swelling of ankles but no albuminuria; on September 18th blood-pressure was 132/82. No albumin or oedema, and on September 25th the second tonephin test was done. Blood-pressure (ordinary reading at rest) 150/80. Base level 100/40; after tonephin systolic pressure rose to 170. Reaction 70 mm.Hg. as compared with 16 mm. Hg. at the first test.

NUMBER 10. Primigravida, aged 36, L.M.P. November 21st to 25th, 1943. First attended clinic on February 3rd, 1944, that is at the 11th week of pregnancy. Healthy woman, urine normal, blood-pressure 124/50. Base level of blood-pressure 118/40. After injection of tonephin systolic blood-pressure rose to 140 mm. Hg. The reaction to tonephin was therefore 22 mm. Hg. On July 20th her blood-pressure was 150/92 and a week later 150/100. There was some oedema of the ankles but no albuminuria. She was admitted to hospital on August 1st, 1944, and the second tonephin test was done next day. The basic level of blood-pressure was estimated as 132/70 and after tonephin the systolic pressure rose to 190. The reaction was therefore 58 systolic compared with 22 systolic at the first test.

These two cases show that the patient who develops pre-eclamptic toxaemia acquires an abnormal sensitivity of the vascular system to the action of pressor substances and that this develops between the early weeks of pregnancy (? 17th week) and the time of appearance of the pre-eclamptic toxaemia.

Attempts were now made to find an answer to the second question, i.e., What causes the sensitization?

Shockaert and Lambillon[14] and de Valera and Kellar[16] found that normal pregnant women gave a lower reaction to tonephin than normal women who were not pregnant; they concluded that there must be in normal pregnancy some inhibiting substance and that the absence of this substance might be the cause of the high reaction found in pre-eclamptic toxaemia. The present writer[17] found that the contrary was the case (see Table I) and that there was not any evidence of the presence of an inhibiting substance.

Certain considerations suggested that chorionic gonadotropin might be the substance responsible for the sensitization. Smith and Smith[18] have reported the presence of abnormally high levels of the anterior pituitary like hormone in the serum and urine of patients with late pregnancy toxaemia and eclampsia and that this increase can be demonstrated 5 or 6 weeks before other signs and symptoms of toxaemia appear. Then there is the fact that in hydatidiform mole in which the output of chorionic gonadotropin is much increased the incidence of pre-eclamptic toxaemia is higher than in normal pregnancy, while some 20 cases of eclampsia have been recorded, though hydatidiform mole usually occurs within the first 3 months of pregnancy. It was therefore decided to try this substance in the first instance and to use synapoidin (Parke, Davis & Co.), a synergistic preparation containing anterior pituitary extract in combination with urinary chorionic gonadotropin. This was preferred to simple chorionic gonadotropin as it would obviously be difficult to inject sufficient of the latter to produce any clinical effect. Several women who were being treated expectantly in the hospital on account of mild antepartum haemorrhage were given daily injections of synapoidin, tonephin tests being done before and after the course of injections in order to test the change in sensitivity, if any. Only women were treated who were likely to be in the hospital for at least 2 or 3 weeks, whose blood-pressure readings had never exceeded 120/80 mm. Hg., whose urine was normal, and who were apart from the mild antepartum haemorrhage apparently

healthy in every respect. In some cases oestrogenic substance (Theelin P. D. & Co.) was used instead of synapoidin but these are few in number and it is doubtful whether enough of the preparation was injected. In one case eucortin was used and the completely negative result obtained is of great interest.

The essential details of the patients treated, the nature and amount of the materials used and the results, as regards sensitization, are as follows:

CASE 1. Mrs. J.E., primigravida, aged 29. Admitted March 3rd, 1945, for slight antepartum haemorrhage at 34th week of pregnancy; no evidence of toxaemia; no extra placental causes of haemorrhage found; no further haemorrhage. Spontaneous delivery at term; mother and child well. Final diagnosis and classification: antepartum haemorrhage of uncertain origin.

17.3.1945. First tonephin test. Base level of blood-pressure 100/44; reaction after tonephin 20 mm. Hg. systolic. Patient then given synapoidin, 1 c.cm. daily for 10 successive days.

26.3.1945. Second tonephin test. Base level of blood-pressure 104/58. Reaction after tonephin 34 mm. Hg. systolic. Patient then had 2 c.c. synapoidin daily for 5 days ending March 30th, 1945.

31.3.1945. Third tonephin test. Base level of blood-pressure 104/46. Reaction after tonephin 40 mm. Hg. Synapoidin continued daily for 6 more days ending April 6th, 1945.

7.4.1945. Fourth tonephin test. Base level of blood-pressure 102/50. Reaction after tonephin 53 mm. Hg.

Delivered April 19th, 1945. There was not, at any time, before or during the treatment evidence of pre-eclamptic toxaemia and the highest recorded blood-pressure was 124/70.

*Comment.* This patient appears to have been sensitized by injection of synapoidin. There was a gradual and consistent rise in the reaction to injection of tonephin from 20 mm. Hg. systolic to 53 mm. Hg.

CASE 2. Mrs. M. P.; primigravida, aged 21. Admitted on April 19th, 1945, for slight antepartum haemorrhage at 31 weeks. No evidence of toxaemia; no extraplacental cause for antepartum haemorrhage found. Treated expectantly. No further haemorrhage. Delivered spontaneously at term. Mother and child well. Final diagnosis and classification antepartum haemorrhage of uncertain origin.

27.4.1945. First tonephin test. Base level of blood-pressure 109/55. Reaction after tonephin 29 mm. Hg. systolic. Patient then given 2 c.cm. synapoidin daily till April 17th, 1945 (42 c.cm.).

18.5.1945. Second tonephin test. Base level of blood-pressure 109/60. Reaction after tonephin 23 mm. Hg. systolic. Synapoidin continued, 2 c.cm. being given daily up to and including May 30th, 1945 (24 c.cm.).

31.5.1945. Third tonephin test. Base level of blood-pressure 110/65. Reaction after tonephin 55 mm. Hg. systolic.

Delivered June 24th, 1945. The highest blood-pressure after synapoidin injection was 130/85 on June 9th, by which time she had received 80 c.cm. According to our standard of normal blood-pressure (120/80) this was raised. It remained about this level till delivery when it fell to 118/90.

*Comment.* This patient seems to have been sensitized by the synapoidin as the reaction to tonephin increased from 29 mm. Hg. systolic to 53. The failure to become sensitized by the time of the second test is hard to explain. It should be recalled, however, that Smith and Smith found that the excess of anterior pituitary-like hormone was present for 5 or 6 weeks before the onset of toxaemia.

CASE 3. Mrs. B. G., aged 25, one previous child. Admitted October 5th, 1945, for slight antepartum haemorrhage at 34 weeks. Extraplacental cause of haemorrhage was not found. There had been no evidence of toxaemia and the first pregnancy had been normal. Treated expectantly in hospital till spontaneous delivery at term on December 14th, 1945. Mother and child well. Final diagnosis and classification—antepartum haemorrhage of uncertain origin.

11.10.1945. First tonephin test. Base level of blood-pressure, 95/38. Reaction after tonephin 40 mm.Hg. systolic. Patient was then given 2 c.cm. synapoidin daily for 11 days up to and including October 21st, 1945.

25.10.1945. Second tonephin test. Base level of blood-pressure, 75/35. Reaction after tonephin 71 mm. Hg. systolic. No further injections given.

*Comment.* The rise in the reaction to tonephin seems to show that this patient was sensitized by synapoidin. The delay of 4 days in carrying out the second tonephin test may have resulted in the recorded sensitization being less than it otherwise would have been.

CASE 4. A. C., aged 34, 2 previous stillbirths due to difficult labour. Contracted pelvis, C.V., 3.6 inches. Admitted on February 28th, 1946, at 38 weeks for slight antepartum haemorrhage. No extraplacental cause for antepartum haemorrhage found. No previous toxaemia; treated expectantly. Caesarean section at term March 22nd, 1946. Mother and child well. Placenta found to be entirely in upper uterine segment.

March 5th 1946. First tonephin test. Base level of blood-pressure, 128/60. Reaction after tonephin, 16 mm. Hg. systolic. Patient then given 12 daily doses of 2 c.cm. synapoidin from March 7th, to March 18th, 1946, inclusive.

21.3.1946. Second tonephin test. Base level of blood-pressure 118/60. Reaction after tonephin 40 mm. Hg.

22.3.1946. Caesarean section. At the operation it was noted that both ovaries appeared to be normal and did not show any evidence of cystic change.

*Comment.* It is doubtful whether any sensitization was produced in this case. It will be noted that the base level of blood-pressure at the second test is 10 mm. Hg., lower than at the first. If the reaction at the second test is counted from the original base level (128) the reaction at this test would only have been 30 mm. Hg. as compared with 16 mm. Hg. at the first. The absence of any visible cystic change in the ovaries is remarkable as it is well known that synapoidin usually causes cystic enlargement of the Graafian follicles. If, therefore, there was sensitization in this case it cannot be explained by stimulation of the follicles to produce excess of oestrogenic hormone. Byrom,[11] however, though he presumed that the gonadotropic hormone with which he produced vascular sensitization in rats acted by stimulating the ovaries to produce oestrin, did not describe any cystic or other morbid change in the rats' ovaries.

CASE 5. B. T., aged 37, para 3. Admitted January 17th, 1946, for antepartum haemorrhage (about 3 ounces) at 34 weeks. No toxaemia (blood-pressure never above 120/80) in this pregnancy. Previous pregnancies said to be normal. Treated expectantly. Delivered spontaneously of a full-time child on March 9th, 1946. Final diagnosis and classification—antepartum haemorrhage of uncertain origin.

24.1.1946. First tonephin test. Base level 108/60. Reaction 22/20. Patient was then given synapoidin daily from January 29th to February 12th, 1946, i.e., 26 c.cm.

12.2.1946. Second tonephin test. Base level 110/60. Reaction after tonephin 24 mm. Hg. systolic. No further treatment was given.

*Comment.* Sensitization does not seem to have been caused in this case.

Case 6. K.S., aged 35, not pregnant. Admitted December 6th, 1945, for investigation and treatment of secondary amenorrhoea which had been present, except for very occasional bleeding from vagina lasting one day, since the first and only pregnancy 3½ years before. Before that pregnancy the periods had lasted 3 days.

The pregnancy and labour had been uncomplicated and there had been no postpartum haemorrhage. Investigations of pituitary fossa and lungs failed to reveal any abnormality. B.M.R. + 14. Lipiodol outline of uterus and appendages showed left Fallopian tube patent, but uterus small. Biopsy of endometrium showed an atrophied mucous membrane with very few glands. Except for the absence of periods there was not any evidence of the presence of Simmond's disease and the patient looked and felt well.

7.12.1945. First tonephin test. Base level of blood-pressure 100/48. Reaction after tonephin 15 mm. Hg. systolic. Patient was then given 14 daily doses of synapoidin 2 c.cm. each, starting on December 15th, 1945.

28.12.1945. Second tonephin test. Base level

of blood-pressure 102/45. Reaction after tonephin 18 mm. Hg., systolic. Synapoidin was continued—2 c.cm. daily for 10 days together with stilboestrol Mg. X daily.

9.1.1946. Third tonephin test. Base level of blood-pressure 102/48. Reaction after tonephin 23 mm. Hg. systolic. Stilboestrol Mg. X and progesterone, Mg. V, were then given daily for 7 days.

17.1.1946. Fourth tonephin test. Base level of blood-pressure, 102/55. Reaction after tonephin, 30 mm. Hg. systolic. No further treatment. Discharged on January 19th, 1946.

*Comment.* There does not seem to have been any sensitization in this case. At no time during treatment did the ovaries become palpably enlarged. No period had occurred when discharged from hospital but on June 5th, 1946, she wrote to say that she had 3 scanty periods at irregular intervals, each lasting from 24 to 72 hours. Perhaps sensitization should not have been expected as the ovaries were probably atrophic. It will be recalled that Byrom concluded that gonadotropic hormone caused sensitization by stimulating ovarian secretion of oestrin.

CASE 7. W. F., age 41. Not pregnant, married 17 years, one induced abortion 10 years ago. Now complains of sterility. Periods regular. Puberty at 11; type, 6/31. Last menstrual period ended March 1st, 1946. No abnormality found in pelvis or elsewhere. Blood-pressure 115/80. Urine normal. Suction curettage on first day of period showed a normal secretory endometrium.

4.3.1946. First tonephin test. Base level of blood-pressure 115/70. Reaction after tonephin 35 mm. Hg. systolic. Patient was then given 1 c.cm. of synapoidin daily from March 25th to 30th inclusive.

1.4.1946. Second tonephin test. Base level of blood-pressure 108/75. Reaction after tonephin 42 mm. Hg. systolic. It is doubtful whether any sensitization occurred in this case.

CASE 8. E. E., aged 29. Sterility. Married 9 years; periods 5-9/2-6 weeks. Last menstrual period May 1st, 1946.

28.6.1946. First tonephin test. Base level of blood-pressure, 100/56. Reaction after tonephin 30 mm. Hg. systolic. One c.cm. synapoidin daily from June 1st to 6th, 1946, inclusive.

7.6.46. Second tonephin test. Base, 116/60. Reaction after tonephin, 12 mm. Hg. systolic.

*Comment.* There was therefore no sensitization in this case. Probably far too little synapoidin was given and for too short a time.

CASE 9. M. C., primigravida, aged 22. Admitted on March 3rd, 1946, at 35 weeks because of slight antepartum haemorrhage. Cervix healthy. No toxaemia. Expectant treatment. Spontaneous delivery at term on April 15th, 1946. Mother and child well. Final diagnosis and classification—antepartum haemorrhage of uncertain origin.

26.3.1946. First tonephin test. Base level of blood-pressure, 108/30. Reaction after tonephin, 42 mm. Hg. systolic. Patient was then given theelin (Parke, Davis & Co.) 1 c.cm. daily from March 29th to April 9th, 1946, inclusive (1 c.cm. = 30,000 international units = 2 mg).

11.4.1946. Second tonephin test. Base level of blood-pressure, 105/45. Reaction after tonephin 60 mm. Hg. systolic.

CASE 10. R. V., age 30. Two previous children. Admitted May 22nd, 1946, at 32 weeks on account of slight antepartum haemorrhage. No toxaemia in this or last pregnancy. First pregnancy said to have been normal. No extraplacental cause of bleeding found.

30.5.1946. First tonephin test. Base level, 100/56. Reaction after tonephin, 25 mm. Hg. systolic. The patient was then given theelin, 1 c.cm. daily from May 31st to June 11th, 1946, inclusive.

12.6.1946. Second tonephin test. Base level of blood-pressure, 102/50. Reaction after tonephin, 32 mm. Hg. systolic.

Eucortin (Allen and Hanbury, a natural extract of adrenal cortex) was then injected, 1 c.cm. daily for 7 days from June 13th, to 19th, 1946. This did not cause any rise of blood-pressure or any visible oedema.

20.6.1946. Third tonephin test. Base level of blood-pressure, 90/46. Reaction after tonephin, 30 mm. Hg. systolic. One c.c. of theelin was again injected daily for 12 days from June 22nd to July 3rd, 1946.

4.7.1946. Fourth tonephin test. Base level, 96/50. Reaction after tonephin, 30 mm. Hg. systolic. There was therefore no demonstrable sensitization caused by the theelin or by the eucortin.

*Comment.* The absence of any rise of blood-pressure or oedema after injection of eucortin is interesting in view of the case reported by Altschule and Zamchek[19] in which a man developed high blood-pressure and gross oedema and anasarca after administration of 5 grammes of common salt daily and 1. c.cm. cortin (Organon, a natural extract of adrenal cortex) daily for 1 week. Mrs. R. V., however, was only receiving the ordinary hospital diet with free use of salt at meals, about 15 grammes daily. The failure of theelin (an oestrogenic substance) to sentitize the patient is disappointing in view of the result of Byrom's experiments on rats already quoted. He states that the minimum effective dose in causing sensitization in the infant rat was about 0.01 to 0.02 mg. daily of an oily solution of oestrone for 5 or more days, with which dose he was successful in 30 out of 32 experiments. Calculated on this basis the amount required for a human female would be about 300 mg. Actually Mrs. M. C. and Mrs. R. V. received only 24 and 48 mg. respectively.

TABLE III.

*Summary of Results Obtained in Attempts to Sensitize the Vascular System by Various Substances.*

| Reference number | Pregnant or not | Substance used | Highest systolic reaction to tonephin before use of sensitizing substance | Highest systolic reaction to tonephin after use of sensitizing Substance |
|---|---|---|---|---|
| 1 | Pregnant | Synapoidin | 20 | 53 |
| 2 | Pregnant | Synapoidin | 29 | 55 |
| 3 | Pregnant | Synapoidin | 40 | 71 |
| 4 | Pregnant | Synapoidin | 16 | 40 |
| 5 | Pregnant | Synapoidin | 22 | 24 |
| 6 | Not pregnant | Synapoidin<br>Stilboestrol<br>Progesterone | 15 | 23 |
| 7 | Not pregnant | Synapoidin | 35 | 42 |
| 8 | Not pregnant | Synapoidin | 30 | 12 |
| 9 | Pregnant | Theelin | 42 | 60 |
| 10 | Pregnant | Theelin<br>Eucortin | 25 | 30 |

## DISCUSSION.

Examination of the case details and of the summary in Table III will show that the most striking results are obtained by the use of synapoidin and that even with that the results are not always consistent. It is doubtful whether oestrogenic substances caused any sensitization though, as we have already seen, Byrom considered oestrin to be the substance responsible for the sensitization that he produced in rats, and that though it could also be produced by injection of gonadotropic hormone this only acted by stimulating the ovary to produce oestrin. He did not, however, describe any cystic change in the ovaries and presumably they were normal.

The work of Smith and Smith[18] suggests that whatever the sensitizing substance be it is not oestrin, for in pre-eclamptic toxaemia

they found it diminished. Gonadotropic hormone, on the other hand, they found to be increased and this increase they were able to demonstrate as much as 5 or 6 weeks before the appearance of other signs of toxaemia. By the administration of oestrogenic substances too they claim to be able to diminish the quantity of gonadotropic hormone and thus prevent toxaemia. If, as Smith and Smith claim, gonadotropic hormone is increased for from 5 to 6 weeks before the appearance of toxaemia it would suggest the use of synapoidin for a longer period than in any of the experiments cited in the text. Meanwhile, so far as conclusions can be drawn from the present investigation, it seems to indicate that chorionic gonadotropic and not oestrogenic hormone is the sensitizing substance. It is probable, however, that neither substance was injected in sufficient quantities.

SUMMARY.

1. Evidence is brought forward that the cause of the hypertension in pre-eclamptic toxaemia is an abnormally increased sensitivity of the vascular system to pressor hormones rather than the presence in excess of the pressor hormone itself.

2. It is proved that this abnormal sensitivity is not inherent or constitutional but that it is acquired at some time between the 17th week and the onset of the clinical signs and symptoms of toxaemia.

3. Clinical considerations and the results of the clinical experiments cited in the text suggest that the sensitizing substance is chorionic gonadotropin rather than oestrogenic hormone or hormone of the adrenal cortex.

I am indebted to Messrs. Parke, Davis & Co. for the supply without charge of the synapoidin and theelin used in the experiment, and to their medical adviser, Dr. Stanley White, for his interest and co-operation.

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# The Superiority of the South African Negro or Bantu as a Parturient

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## PART III.—A COMPARISON OF BANTU AND EUROPEAN PARTURITION IN TWO SERIES DERIVED FROM THEIR RESPECTIVE ANTENATAL CLINICS.

### INTRODUCTION.

IT is difficult to judge a parturient fairly when, as is the case in cities, the obstetrician's experience is derived from a hospital practice. The hospital is almost invariably the scene at which trained observers in this country can study labour in the South African Negro or Bantu. An opportunity of making observations in domiciliary midwifery on Bantu parturients has been offered. Seven years ago an antenatal clinic was started in a large native township, and it is now possible to assess labour as it occurred among the Bantu women who attended the clinic.

During the course of the work done, a strong impression was gained that the Bantu parturient was far more efficient than the European, and that she appeared to be much better adapted to the strain of labour, requiring instrumental or other operative delivery infrequently. This was the more surprising, because our studies have shown the Bantu head at birth to be as large as that of the European, and the Bantu pelvis to be slightly smaller. Moreover, there is in the Bantu a range of small pelves which is much lower than that of the non-pathological European girdle, and the incidence of these small pelves is relatively high.

A comparison of the labours recorded concerning patients from our European antenatal clinic and those from the Bantu clinic has been made for the quinquennial period 1940–1944, in order to arrive at an assessment of the 2 series of women relative to their success in parturition.

### MATERIAL AND METHODS.

*Material.*

A comparison between Bantu and European labours has been made on the basis of material dealt with at the antenatal clinic. The analysis includes all cases seen over a period of 5 years (1940–1944) at:

1. The Municipal antenatal clinic for European Women in Johannesburg. While 5,059 patients are included in this survey, this does not represent the total number seen at the clinic during 1940–1944. Owing to a delay of 1 year after most of the antenatal cards had been studied, a difficulty arose which made it impossible to be precise about the inclusion of approximately half of the 1940 cards. These were, therefore, omitted, and those of the last quarter of 1944.

2. Alexandra Township. There were 1,433 women attending the local antenatal clinic during 1940–1944. The township is situated on the outskirts of Johannesburg and has a population of about 80,000. The men and some women are occupied in the city or its suburbs, but not on the gold mines; and there are numerous schools and churches in the township which is owned

by the inhabitants. There is a well-established polyclinic from which *inter alia* a district service is operated. Students are in residence here and attend the clinic, there are several doctors on the permanent staff, and the full-time personnel of the University Department of Obstetrics and Gynaecology conduct the antenatal clinics. Midwives consult the obstetricians concerning cases of abnormal labour, and these are transferred to the Bridgman Memorial Hospital (Maternity) when necessary. No instrumental or other complicated deliveries are effected on the district.

The women of the township are under European influences and their mode of life is similar to that of any urbanized European community. In spite of this, they are still Bantu, essentially primitive, and their instincts are still those of the women living under tribal conditions. Recently an increasing number of "raw" newcomers to the city has been attending—individuals who, in no obvious manner, conform to European standards and who were certainly reared in Native territories. Concerning the others, the less primitive women, it is not known whether they were born here or in their ancestral countries. It must be pointed out that Johannesburg began as a mining camp only 59 years ago.

*The European Series.*

There were 5,059 patients who attended the clinic. Of these 3,802, or 75.2 per cent, were delivered at the Queen Victoria Hospital. The remainder had their babies at home under the care of the Municipal District Service, and in the event of any abnormality developing during labour would have been sent to hospital. Of the 3,802 hospital women 1,564 or 41.2 per cent were primigravidae. If 1,564 primigravidae be taken against 5,059, the total for the series, the percentage of primigravidae seen was 30.93. The true figure is slightly higher than this, because a small number of primigravidae was delivered on district. These were normal cases and cannot affect the analysis, as will be shown later.

*The Bantu Series.*

1,433 patients attended the clinic during the 5 years under consideration. Of these, 5 women aborted, and the records of 3 could not be traced. Of 1,425 patients who had viable babies 364, or 25.58 per cent, were primigravidae.

*Methods.*

The method of analysis followed the principles of statistics, and comparison between European and Bantu incidence was based on statistical significance. No apology will be offered for illustrating how it is decided whether a difference between percentage values for the two racial groups is "significant" or whether it may have arisen by chance. Therapeutic trial is often based on about 15 cases receiving therapy, and 15 controls. If the control group shows a few more successes than the therapy group, it has been thought that the therapeutic measures have been shown to lack value. This conclusion is not necessarily correct for, on the play of chance, certain differences must be expected. These chance differences become more unexpected as the groups observed become smaller.

In comparing 2 percentages, the standard error of each must be considered. This is given by the factor $\sqrt{\frac{p \times q}{n}}$, where $p$ might be the percentage of European women requiring operative delivery and $q$ the percentage not requiring operative delivery, $n$ being the number in the sample. The standard error of the difference between European and Bantu percentages may be shown to be $\sqrt{\frac{p_1 \times q_1}{n_1} + \frac{p_2 \times q_2}{n_2}}$

where $n_1$ and $n_2$ are the numbers in the two samples, and $p$ and $q$ as above. If all circumstances were equal, it would be reasonable to expect the difference between European and Bantu percentages to be 0; but we might quite easily, on the play of chance, obtain a difference equal to plus or minus twice the standard error of the difference. Therefore, if the difference is more than twice its standard error, the probability is in favour of this difference not having arisen by mere chance. The difference may then be claimed to be "significant," though the actual origin of this "significance" has to be sought elsewhere.

It will be obvious that the greater the numbers in the samples, the more likely is it that significance for the difference, if any exists, will be established. Thus the percentage difference between the two races here studied for operative interference was $5.24 - 0.558 = 4.682$. The standard error of this difference is

$$\sqrt{\frac{5.24 \times 94.76}{5059} + \frac{0.558 \times 99.442}{1433}} = 0.37.$$

The difference of 4.682 is 12.77 times its standard error (0.37) and is, therefore, significant. If the samples were in the same proportion, say 10 Bantu and 35 Europeans, the standard error of the difference works out at 4.44. This standard error is almost equal to (1.05 times) the difference between the two samples. As a difference which is even twice its standard error may have arisen by chance, significance could not be claimed in the case of the small samples. It is to be noted, however, that with the samples of 1,433 and 5,059, the difference is in fact highly significant.

## Analysis.

Because 75.2 per cent of Europeans, and only 2.23 per cent of Bantu were delivered in hospital, it is obvious that the analysis of abnormal deliveries must be based on the totals of 5,059 European and 1,433 Bantu.

There is a significant difference (4.04 times its standard error) between the percentages of primigravidae in the two series. This means that any character which may be influenced by the fact that a patient is either a primigravida or a multipara cannot be considered on the basis of incidence percentage of the whole series, i.e. Bantu series or European series. The European primigravid incidence is about 6 per cent higher than that of the Bantu. Therefore there is a slightly greater probability of dystocia in the European than in the Bantu.

| | | | |
|---|---|---|---|
| *European* | Total | 5059 | |
| Total primigravidae | | 1564 | 1564 in hospital |
| Total multiparae | | 3495 | 2238 in hospital |
| Total hospital cases | | | 3802 or 75.2 per cent |
| *Bantu* | Total | 1433 | |
| Total primigravidae | | 364 | 12 in hospital |
| Total multiparae | | 1069 | 20 in hospital |
| Total hospital cases | | | 32 or 2.23 per cent |

1. *Operative Deliveries.* These include all assisted deliveries such as forceps, breech deliveries, and Caesarean section.

| | European total 5059 | | Bantu total 1433 | |
|---|---|---|---|---|
| | No. | Percentage of total | No. | Percentage of total |
| Hospital cases | 3802 | 75.2 | 32 | 2.23 |
| Operative cases | 265 | 5.24 | 8 | 0.558 |
| Percentage of hospital cases that had operative delivery | | European | | 25.00 |
| | | Bantu | | 6.96 |

Percentage difference for operative deliveries $4.682 \pm 0.37 = 12.77 \times$ standard error. There is, therefore, a highly significant difference showing that the European requires assistance at delivery more often than the Bantu.

2. *Forceps Delivery.*

(a) *High, mid, and low forceps delivery.*

(i) Primigravidae and multiparae.

| | | |
|---|---|---|
| European | 73 | primigravidae |
| | 19 | multiparae |
| Total | 92, or 1.82 per cent | |
| Bantu | 2 | primigravidae |
| | 1 | multipara |
| Total | 3, or 0.21 per cent | |

Total percentage difference = 1.61 ± 0.223
= 7.22 × standard error

(ii) Primigravidae only.

| | |
|---|---|
| European | 73, or 4.67 per cent of 1564 |
| Bantu | 2, or 0.55 per cent of 364 |
| Difference | 4.12 ± 0.66 |
| | = 6.26 × standard error |

(iii) Multiparae only.

| | |
|---|---|
| European | 19, or 0.544 per cent of 3495 |
| Bantu | 1, or 0.094 per cent of 1069 |
| Difference | 0.450 ± 0.156 |
| | = 2.89 × standard error |

(b) *Low forceps delivery only.*

(i) Primigravidae only

| | |
|---|---|
| European | 53, or 3.388 per cent of 1564 |
| Bantu | 1, or 0.275 per cent of 364 |
| Difference | 3.113 ± 0.535 |
| | = 5.82 × standard error |

The above figures illustrate, first, the low forceps-rate of 1.82 per cent for Europeans. For some years it has been urged that our European forceps-rate is too low, and that an increase would be an advantage to resident students without militating against the principles of good obstetric practice. Compared with this low incidence in the European, the need for forceps delivery in the Bantu is significantly much less frequent, being 0.21 per cent as compared with over 5 per cent in most European communities elsewhere.

There is a statistical objection to grouping parous and primigravid women together because of the reason mentioned in the section on Method: there is a significantly higher percentage of primigravidae in Europeans than in the Bantu, and the forceps-rate must always be higher in primigravidae. No claim will, therefore, be made for the difference which is as high as 7.22 times its standard error. It is seen, however, that for primigravidae alone (2, a, ii) there is a highly significant difference between the races, showing how infrequently forceps delivery is required in the Bantu. The corresponding figures for multiparae—difference = 2.89 × standard error—is probably significant. There was only one case of forceps in 1,069 Bantu, and it is likely that in 2,000 Bantu there still would have been only one. It is submitted that the difference found is significant.

Forceps deliveries were recorded as being "low", "mid", and "high". The most reliable variety from the point of records is the "low" operation. Moreover, it was thought that a comparison on this basis would indicate whether the Bantu had as much difficulty in driving the head over the perineum as is known to be the case in the Europeans. The figures show that the low forceps operation was performed significantly more often in the European than in the Bantu.

3. *Caesarean Section.*

| | |
|---|---|
| Total European | 28, or 0.554 per cent of 5059 |
| Total Bantu | 3, or 0.209 per cent of 1433 |
| Difference | 0.345 ± 0.159 |
| | = 2.17 × standard error |
| European primigravidae | 10, or 0.64 per cent of 1564 |
| Bantu primigravidae | 2, or 0.55 per cent of 364 |
| Difference | 0.09 ± 0.44 |
| | = 0.205 × standard error |

No statistical significance can be claimed for the above figures. This would mean that European and Bantu rates for Caesarean section were similar. It is probably

justifiable to group primigravid and multiparous subjects, because section is not done more frequently on primigravidae: the reasons for the operation are so diverse that a mixed sample consisting of women pregnant for the first or a subsequent time may well be compared with another sample similarly composed. If this principle be admitted, then there is possible significance in the lower Bantu rate for the total series. It should be noted that the European rate for Caesarean section is very low.

4. *Maternity Mortality.*

| | |
|---|---|
| European | 6, or 0.119 per cent of 5059 |
| Bantu | 2, or 0.1394 per cent of 1433 |
| Difference | 0.0204 ± 0.11 |
| | = 0.19 × standard error |

The difference is not significant. The European death-rate of just over 1 per thousand is unusually low.

5. *Foetal Mortality.*

It is necessary at this stage to consider the foetal death-rate because of the fortitude shown by the Bantu mother in delivering herself. The analysis thus far has demonstrated the superiority of the Bantu woman as a parturient. The question arises, therefore, whether as a result of these vigorous Bantu labours, at which there is so seldom any assistance, there is not a high foetal mortality.

(a) *Stillbirths* (excluding multiple pregnancies).

| | |
|---|---|
| European | 96, or 1.910 per cent of 5023 |
| Bantu | 49, or 3.505 per cent of 1398 |
| Difference | 1.595 ± 0.528 |
| | = 3.02 × standard error |

This difference is significant. The reason for excluding multiple pregnancies from analysis 5(a) is that there is a mortality amongst twin and triplet foetuses which invalidates sound comparison. The same does not apply with equal force to premature births for two reasons: one is that the premature foetus, unless macerated, is usually born alive; the second is that there is no reliable criterion for prematurity, and hospital records are misleading on this point.

Although the Bantu stillbirth-rate is significantly higher than the Johannesburg European, it is low as compared with other large European series. The most favourable figure encountered is that of De Lee,[1] who showed that at his Chicago Hospital the figure had been reduced to 2.14 per cent in 51,422 births. The Bantu and Chicago percentage difference is 2.76 times its standard error. This is probably significant, though the significance is of a low order, a fact which is further illustrated by a comparison with other white race figures. Thus the British figure of 4 per cent is higher than that of the Bantu at 3.5 per cent. Figures from the U.S.A. and Germany vary between 4 and 5 per cent,[2] and it is noteworthy that as early as 1877 the stillbirth-rate in the U.S.A. was 5 per cent.[3] It is seen, therefore, that in spite of the lively Bantu labours, the foetal mortality is low: it is significantly higher than that of the Johannesburg European series, because of the fact that the latter shows even a lower stillbirth-rate than that of De Lee.[1]

(*b*) *Neonatal mortality.* The European and Bantu percentages for recorded neonatal deaths were respectively 0.74 and 0.86. The true percentage must be higher in each case, because the recorded deaths have occurred only during the lying-in period.

6. *Uterine Action.*

(*a*) *Uterine Inertia.* The recorded figures for inertia have been found too unreliable to analyse. The error is due to omission of cases,

(*b*) *Manual removal of the placenta.*

European 48, or 0.95 per cent of 5059
Bantu 3, or 0.209 per cent of 1433

Difference 0.741 ± 0.185
=4.02 × standard error

The European figure for manual removal of the placenta is reasonable, and the above difference indicates that this operation is rarely required in the Bantu.

(*c*) *Postpartum haemorrhage.* The amount of blood loss was measured precisely in the case of those Europeans who were delivered in hospital. European cases on district with pronounced loss were transferred to hospital. For this analysis a haemorrhage of 40 ounces or more was considered. Amongst primigravidae there were 42 and amongst multiparae 60 women who had a haemorrhage ranging between 40 and 100 ounces. The total of 102 represents 2.02 per cent of the whole series.

On the district 97.7 per cent of Bantu women were delivered, and records relating to postpartum haemorrhage could not be used for statistical purposes. The general impression is that postpartum haemorrhage is uncommon, and it is certain that very few cases required blood transfusion.

## Miscellaneous.

7. *Breech Presentation.*

European 89, or 1.75 per cent of 5097
Bantu 19, or 1.31 per cent of 1446

Difference 0.44 ± 1.11
= 0.39 × standard error

The difference is not significant.

8. *Multiple Pregnancy.*

Twins

European 36, or 0.712 per cent of 5059
Bantu 16, or 1.120 per cent of 1433

Difference 0.408 ± 0.315
= 1.3 × standard error

The difference is not significant.

In addition to the twins, there was one set of triplets in each series. The Europeans were all stillborn, and the Bantu triplets were alive at 2 years of age.

## Deaths.

*European.* There were 6 deaths.

(i) A para 3 died on the 7th day of the puerperium. She had had an excessive postpartum haemorrhage, and the placenta was removed manually.

(ii) A para 1 died on the 18th day of the puerperium as the result of puerperal sepsis. The delivery was normal, with the birth of a live child.

(iii) A multipara with a twin pregnancy died of obstetric shock a few hours after labour.

(iv) A primigravida died undelivered as a result of congestive cardiac failure. She attended the antenatal clinic only once, 2 weeks before admission and 4 weeks before her death.

(v) A primigravida died 1 hour after low forceps delivery. On admission she had gross cardiac failure, and autopsy showed the presence of acute rheumatic endocarditis. The patient had been sent from a long distance, and was transferred to hospital from the clinic without delay. Labour commenced 2 days after admission.

(vi) A primigravida died 14 hours after Caesarean section. The patient had mitral and aortic valve incompetence, and was admitted in early cardiac failure. She was in labour with the head above the brim, and it was thought that Caesarean section would be the best method of treatment. Ten hours later she developed left-sided failure and died 4 hours later.

The first three deaths were preventable, and the last three were cardiac cases. Cases iv and v attended the antenatal clinic only once, and Case iv did not carry out the instructions given at the clinic: she failed to

report at the hospital as an in-patient and was not seen for a month prior to admission.

*Bantu.* There were 2 deaths.

(i) A primigravida aged 17 years was admitted to hospital in cardiac failure with swollen feet, a moderate degree of cyanosis and dyspnoea. She had a normal delivery after a prolonged labour, developed lobar pneumonia, and died 4 days after delivery.

(ii) A multipara was delivered of a macerated foetus and died soon after delivery. The cause of death was not obvious; but the lochia were very offensive and frothy, and obstetric shock was thought to be an important factor in causing the death of this toxic patient.

## Discussion.

The antenatal clinic figures shown in this paper compare very favourably with those reported elsewhere. The main feature to emerge from the analysis is the marked ability of the Bantu woman to deliver herself without assistance.

The Bantu female pelvis is slightly smaller than that of English women. Ince and Young[4] found the average area of the brim in London English women to be 126.8 sq. cm., whereas the corresponding Bantu figure was 101.23, the largest brim of a series of 67 dry pelves[5] being equal to Ince and Young's average. The size of the Bantu head at birth was shown by Heyns[6] to be equal to that of white races. Therefore, all things being equal, the Bantu parturient should have a lower incidence of spontaneous births than the European woman.

Whereas 5.24 per cent of European parturients required operative interference, only 0.558 per cent of the Bantu women required assistance at delivery. The percentage difference of 4.682 is 12.77 times its standard error, and this is highly significant. Thus, even though she has to expel a head of the same size as that in the European through a birth canal which is smaller than that of the European, the Bantu parturient shows a pronounced superiority in labour. This is further borne out by the significantly low forceps-rate of 0.21 per cent for the Bantu series. When low forceps delivery in primigravidae alone is considered, it is found that the European requires instrumental delivery more often than the Bantu with a 3.113 per cent difference which is 5.82 times its standard error. This significant difference emphasizes the fact that the Bantu is better able to drive the head over the perineum than is the case with the European. There is no doubt that the European, if it is a matter of necessity, can expel the head through the pelvic outlet; but in the case of the Bantu woman there is, in her opinion, no alternative to spontaneous labour: she believes that failure to deliver herself means death. This outlook can have only a salutary effect on the process of parturition, and avoids much of that interference in the European which the obstetrician knows to be dangerous and fundamentally unnecessary. There can be little doubt that civilization and too great a dependence on the doctor has reduced the efficiency of the European parturient.

Heyns[7] has shown that, whereas the greatest cross-section of the well-flexed foetal head is about 70 sq. cm., the Bantu woman can, nevertheless, expel such a head through pelvic planes less than 80 sq. cm., and in a few cases even less than 70 sq. cm. This is illustrated by a remarkable case of the present series. This was a woman of 27 years who had had a Caesarean section for her first pregnancy. It had been explained to her that another section would be absolutely necessary, for the pelvis had been found to have the following dimensions:

Areas (sq. cm.): cavity 71.7, brim 75.4, outlet 64.5.

Brim index: 98.9 (conjugate 9.5 cm., transverse 9.6 cm.).

Outlet diameters: intertuberal 10.1 cm., interspinal 10.4 cm., and pubosacral 9.1 cm.

The patient sent for help after the baby had been born. There was extensive perineal laceration. The baby was a female weighing 6½ pounds, and the head was moulded into a misshapen mass. The infant died an hour after birth.

Several of these interesting experiments became possible in Alexandra Township. It would be inhuman to allow trial labour in such cases, but in their desire to deliver spontaneously these women often avoided sending for help until labour was well advanced or completed. This has led to the view that there is danger in allowing uterine powers to have full sway under such circumstances, because of the risk to the foetus. This makes contracted pelvis as an indication for Caesarean section more difficult to assess, it being obvious that mere ability or failure on the part of the mother to deliver herself is no criterion having regard to the safety of the foetus.

In view of these facts, consideration of maternal and foetal mortality is demanded. In this series there was a Bantu maternal death-rate of 1.394 per thousand, and a Bantu stillbirth-rate of 3.505 per cent. These figures have been shown to compare favourably with the best figures from Europe and America.

From the above analysis it must be concluded that the Bantu parturient exhibits considerable superiority over the European. This refers to the Bantu under home conditions. It will now be necessary to compare two large series of hospital patients, Bantu and European, in order to assess the effect of hospitalization on the emotional reactions of the parturient. It is our impression that in hospital the Bantu is a less efficient parturient than the European woman, whereas we have proved that in her own home she is greatly superior.

## Summary.

1. An analysis has been made of 1,433 Bantu and 5,059 European antenatal patients seen over a period of 5 years.

2. A highly significant statistical difference for operative delivery was found, and shows that the European requires assistance at delivery more often than the Bantu.

3. Maternal and foetal mortality were low in both series.

4. Other features concerning parturition were analysed; and it has been proved that the Bantu in her own home is a more efficient parturient than the European woman.

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# The Blood in Pregnancy

## PART II. THE BLOOD VOLUME, CELL VOLUME AND HAEMOGLOBIN MASS

BY

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THE blood volume of normal adults has generally been assumed to bear a very constant relation to the body size, except in the case of pregnancy. Here it has long been known that changes in volume occur, but the extent of these changes has not been clearly established. Early work on the problem was subject to the criticism that the methods were unreliable, nevertheless it was clear in each case that a substantial increase in the blood volume did occur during pregnancy.[1, 2, 3]

All criteria of the normality of the blood constituents are based on their level in the blood, but it seems probable that the most important factor physiologically is their level in the whole body which they have to supply. So long as the blood volume bears a constant relation to body size, the blood level will give a quantitative indication of the amount of the blood constituents in the body, but when the blood volume varies, as it does in pregnancy, it is obvious that the relationship will not hold, and it will not be possible to deduce the amounts present in the body from their levels in the blood.

The present work was undertaken to investigate the extent of the variations in blood volume which occur during pregnancy, to discover how these variations affect the total amounts of haemoglobin and red blood cells, and whether their levels in the blood, under the new conditions, give any indications of their levels in the body.

It was first necessary to confirm the fact of a constant relationship between blood volume and body size in non-pregnant women and to decide what measurement gave the best criterion of size. The first study of this subject was that made by Rowntree and Brown[4] who investigated 49 men and 25 women and showed that the blood volume bore a constant relation to the surface area, which is a function of the height and weight. The relation between blood volume and weight was not so constant. Gibson and Evans[5] studied 49 men and 41 women and considered the relation between the blood volume, height, weight and surface area. They did not investigate statistically which measurement gave the best correlation, but if this is done it is apparent that the correlation of blood volume with surface area is slightly better than that with weight. These results and those to be reported suggested that the surface area was the most useful criterion of body size.

The question of the criterion of body size

during pregnancy is complicated by several factors. The weight of the pregnant woman includes that of the foetus which has its own independent blood supply, so that this measurement gives too high values. In spite of this fact numerous workers have used weight, but Dieckmann and Wegner[2] when they found that in many cases the concentration of blood per kilogram apparently fell during pregnancy, abandoned all attempts to allow for changes in the maternal size and considered all results from the point of view of the percentage changes in absolute amounts. Some allowance for maternal changes and for individual variations in size seems, however, desirable, and here the surface area has been used in pregnant, as in non-pregnant women. The error due to inclusion of foetal tissue is not so great as with weight, as the formula from which the surface area is derived depends on the height more than on the weight

$$(\text{Area} = \text{Weight}^{0.425} \times \text{Height}^{0.725} \times C).$$

It is realized that this formula, owing to changes of shape during pregnancy, probably does not give the actual surface area, but it was considered to give the most satisfactory values available.

Part A of this work records the results of an investigation of the blood volumes of 20 normal non-pregnant women. The relation of the blood volume to body size is considered, together with the relation between the levels of haemoglobin and cells in the blood and in the body.

In Part B the results of blood volume and full blood investigations of 20 women at 3 different stages of pregnancy are reported. The changes in absolute amounts of blood, haemoglobin and cells are considered, together with their changes in concentration in the body and the changes of concentration of haemoglobin and cells in the blood.

## Methods.

The blood volumes were estimated by the dye method, using Evans blue (T-1824) and the technique described by Davis.[5a] The subjects after a breakfast containing no fat, came to hospital and were rested for 30 minutes before the test. While still recumment, 5 ml. of a 240 mg. per 100 ml. solution of dye in normal saline was injected into one arm vein and blood removed from the other arm 10 minutes later. The dye concentration in the serum was estimated with a 'Spekker' photo-electric absorptiometer, by comparison with a standard solution made up with serum obtained before dye injection. From this the plasma volume was calculated. Blood volumes obtained by this method theoretically may be accurate to within 5 per cent. The normal blood volume can thus be estimated within 200–250 ml.

Blood was collected at the first venepuncture in a Wintrobe tube and used for determination of the haemoglobin concentration, red blood cell count and haematocrit. The haemoglobin was determined with a Haldane haemoglobinometer, the apparatus being standardized by the National Physical Laboratory. The Haldane haemoglobinometer was calibrated so that 100 per cent represented 13.8 g. per 100 ml. From the haematocrit and plasma volume were calculated the total blood volume and cell volume and from the haemoglobin concentration and blood volume the total haemoglobin mass.

It has recently been suggested by Cruikshank and Whitfield[6] that some of the dye when first injected is taken up by the reticulo-endothelial system and does not appear in the circulating blood. If this is so the blood volumes obtained will be too high. The conclusion was based on animal experiments and would not appear, from the following test, to hold for man. Three

normal women received 2 injections of 12 mg. of dye at 10 minutes intervals. The concentrations of dye 10 minutes after the first injection and 10 minutes after the second were 0.55 and 1.11 mg./100 ml., 0.48 and 0.90 mg./100 ml. and 0.58 and 1.10 mg./100 ml. The concentration in the second sample was thus in every case approximately twice that in the first, and there was no evidence that any of the first lot of dye had not entered the circulation.

It has been suggested that the rate of mixing of dye in the plasma and its rate of elimination differ from the normal in pregnancy. Thus Graff *et al.*[7] found that in 2 pregnant women the mixing time of vital red was prolonged from the normal of 6 minutes to 9 and 10 minutes. Before mixing was complete, high concentrations of dye were present. In order to investigate these points 3 women in the third trimester of pregnancy had samples of blood removed at varying times after the dye injection. The following dye concentrations per 100 ml. of blood were found: first case, 5 min., 0.41 m.g.; 10 min., 0.36 mg.; 20 min., 0.37 mg.; second case, 5 min., 0.29 mg.; 10 min., 0.24 mg.; 20 min., 0.24 mg.; third case, 10 min., 0.29 mg.; 15 min., 0.29 mg. The first 2 cases showed the initial high concentration, before mixing was complete, but by 10 minutes this was over and 15 and 20 min. samples showed no further dilution. The fact that there was no fall in concentration in the second 10 minutes indicated that during pregnancy the dye was not removed from the circulation with abnormal rapidity. If a loss occurs to the placental circulation it must either be immediate or else very slow. It should be noted that Thomson *et al.*[3] could find no Evans blue in amniotic fluid, cord blood or placental membranes when it had been injected into the maternal circulation shortly before parturition.

## Non-pregnant Women.

The details of the findings are shown in Table I. There were considerable variations in the total blood volumes of the 20 women investigated, but these were closely correlated with variations in the surface area (correlation coefficient 0.898, standard error 0.190). There was, therefore, little variation in the blood volume per square metre, the mean value for which was 2,660 ml. with a standard deviation of 163 ml. The correlation between blood volume and body weight was not as close (correlation coefficient 0.694, standard error 0.170). The mean blood volume per kilogram was 74.5 ml. with a standard deviation of 6.8 ml.

The mean blood haemoglobin level of the cases was 93 per cent, standard deviation 8.65 per cent. There was a slight tendency for low haemoglobin levels to occur when the blood volumes were high, but the correlation coefficient of −0.129, standard error 0.235, was not significant. The mean total haemoglobin mass was 340 g. per square metre, standard deviation 35 g. There was a close correlation between the level of haemoglobin in the blood and that in the whole body, the correlation coefficient being 0.843, standard error 0.127.

The mean haematocrit was 42.3 per cent, standard deviation 3.9 per cent. There was no correlation of haematocrit with blood volume. The mean total cell volume was 1,130 ml. per square metre, standard deviation 115 ml. The proportion of cells in the blood was correlated with the cell volume per square metre, the correlation coefficient being 0.817, standard error 0.136.

## Conclusions.

The blood volumes of 20 normal non-pregnant women were found to vary

with their surface area, the mean amount per square metre of surface area being 2,660 ml. Since this relationship was reasonably constant, the level of cells and haemoglobin in the body was proportional to their level in the blood.

The value of 2,660 ml./sq. m. (standard deviation, 163) may be compared with that found by Rowntree and Brown[4] in 25 normal women, which was 3,130 ml./sq. m. (standard deviation, 276) and also with the figure of 2,460 ml./sq.m. (standard deviation, 240) which may be calculated from the results of 39 cases reported by Gibson and Evans.[5] With the latter figure there is a fair agreement but that of the earlier workers is considerably higher.

### Pregnant Women.

Twenty women were followed throughout normal pregnancies. They were all but one attending the hospital antenatal clinic and were chosen as being normal cases in the early months of pregnancy. The number able and willing to co-operate was not large and for this reason it was necessary to use some cases seen first as late as the 16th week. First tests were made between the 8th and 16th week, mean 12.4 weeks; second, between the 20th and 27th weeks, mean, 24.2 weeks and third between the 33rd and 38th weeks, mean 35.6 weeks. The ages of the women varied from 20–39 years, mean 28.2 years. Seventeen were primiparae and 3 multiparae.

Table I.

*The Surface Area, Blood Volume and Haemoglobin and Cell Concentrations in 20 Normal Women.*

| Case No. | Surface area sq.m. | Blood volume, ml. | Blood volume, ml./sq.m. | Haemoglobin, per cent | Haematocrit, per cent |
|---|---|---|---|---|---|
| 1. | 1.36 | 4100 | 3000 | 100 | 47 |
| 2. | 1.47 | 3800 | 2550 | 92 | 43 |
| 3. | 1.48 | 4100 | 2750 | 78 | 38.5 |
| 4. | 1.50 | 3900 | 2600 | 98 | 45 |
| 5. | 1.51 | 3900 | 2600 | 92 | 40 |
| 6. | 1.52 | 3800 | 2500 | 98 | 46 |
| 7. | 1.53 | 3800 | 2500 | 94 | 44 |
| 8. | 1.54 | 4100 | 2650 | 82 | 37 |
| 9. | 1.58 | 3900 | 2450 | 98 | 43.5 |
| 10. | 1.59 | 4200 | 2650 | 88 | 39 |
| 11. | 1.60 | 4100 | 2550 | 112 | 49 |
| 12. | 1.63 | 4100 | 2500 | 76 | 35.5 |
| 13. | 1.64 | 4100 | 2500 | 96 | 42 |
| 14. | 1.71 | 4600 | 2700 | 92 | 41 |
| 15. | 1.71 | 4700 | 2750 | 96 | 44 |
| 16. | 1.72 | 4500 | 2600 | 98 | 49 |
| 17. | 1.77 | 4900 | 2800 | 104 | 45 |
| 18. | 1.89 | 5600 | 2950 | 82 | 38 |
| 19. | 1.90 | 5700 | 3000 | 90 | 40 |
| 20. | 1.91 | 5100 | 2650 | 90 | 39 |

(1) *The Concentration of Haemoglobin and Cells in the Blood.*

The mean haemoglobin concentration, haematocrit and red blood cell count of the women at each of 3 tests are shown in Table II, together with the mean corpuscular haemoglobin content, mean cell haemoglobin, colour index and mean cell volume.

per cent. This fall was parallel with the fall in haemoglobin as was shown by the fact that the mean corpuscular haemoglobin, or concentration of haemoglobin in the cell mass, altered little, it was 30.4 per cent, 31 per cent and 31.1 per cent at the 3 tests. Individually there was little variation in the M.C.H.C. as is shown by the small standard deviation.

TABLE II.

*The Mean Blood Findings in 20 Women at Three Stages of Pregnancy.*
Cases having iron in parenthesis.

| | Mean duration of pregnancy | | | | |
|---|---|---|---|---|---|
| | 12.4 weeks | 24.2 weeks | | 35.6 weeks | |
| No. | 20 | 20 | (3) | 20 | (4) |
| Haemoglobin g./100 ml. ... | 12.0 | 11.5 | | 11.3 | |
| Standard deviation ... | 1.3 | 1.2 | | 0.8 | |
| Per cent of normal ... | 86.6 | 82.6 | (83.3) | 82.1 | (83.5) |
| Haematocrit, per cent ... ... | 39.2 | 37.0 | (37.8) | 36.4 | (36.7) |
| Standard deviation ... | 3.2 | 2.0 | | 2.2 | |
| R.B.C.s m./c.mm. ... ... | 4.47 | 4.15 | (4.21) | 4.15 | (4.09) |
| Standard deviation ... | 0.42 | 0.25 | | 0.39 | |
| M.C.H.C. g./100 ml. ... ... | 30.4 | 31.0 | (30.3) | 31.1 | (31.4) |
| Standard deviation ... | 1.8 | 1.3 | | 1.7 | |
| M.C.H. yy ... ... ... | 26.2 | 27.4 | (27.5) | 27.3 | (28.2) |
| Standard deviation ... | 2.6 | 2.0 | | 2.1 | |
| Colour index ... ... | 0.97 | 1.00 | (1.02) | 1.00 | (1.04) |
| M.C.V. cμ ... ... ... ... | 87.9 | 88.5 | (90.4) | 88.1 | (90.2) |
| Standard deviation ... | 6.3 | 6.2 | | 7.2 | |

*Haemoglobin concentration.* This fell throughout pregnancy in those cases with initially high values and remained constant when the initial values were low. Five cases showed a rise or no change between the first and last tests, the remainder showed a fall. The mean values at the 3 tests were 86.6 per cent, 82.6 per cent and 82.1 per cent, or 12.0 g., 11.5 g. and 11.3 g. per 100 ml.

*Haematocrit.* The volume of cells in the blood fell during pregnancy in 18 out of the 20 cases. The mean figures at the 3 tests being 39.2 per cent, 37.0 per cent and 36.4

*Red blood cells.* These also fell, in 16 out of the 20 cases, and the means at the 3 tests were 4.47 mil., 4.15 mil., and 4.15 mil. The fall was similar to that of haemoglobin concentration, the mean cell haemoglobins being 26.2 yy, 27.4 yy and 27.3 yy, and the colour indices 0.97, 1.00, and 1.00. There was thus no tendency for hypochromia to develop. The lowest colour indices at the final test were 0.87 and 0.88, and all the others were greater than 0.90. The mean cell volumes were 87.9 cμ, 88.5 cμ and 88.1 cμ. There was thus no appreciable change in the cell size.

*Cases who received Iron.*

Two of the women, whose haemoglobins when first seen were 72 per cent and 62 per cent respectively, were treated with iron. Two others were given iron by their own doctors. The mean values of these cases are shown in Table II in parenthesis. The case with an initial haemoglobin of 62 per cent and colour index of 0.74, thereafter had a haemoglobin of 94 per cent and colour index over unity. In the others, who did not originally show hypochromia, the haemoglobin did not rise above 82 per cent and a comparison with other cases with similar values makes it extremely doubtful whether the iron medication had any effect.

*Blood volume.* There was an increase in the blood volume between the first and third tests in every case. This increase was not always steady throughout, in 4 cases the volume fell between the first and second tests and in another 3 it fell between the second and third tests. The increase was extremely inconstant in amount, the difference between the first and third tests ranging from 200 ml. to 2,800 ml. The mean values at the 3 tests were 4,300 ml., 4,900 ml. and 5,400 ml.

*Haemoglobin mass.* There was a significant increase in the haemoglobin mass between the first and third tests in 14 out of the 20 cases. The increase varied from 50–360 g. In the remaining 6 cases the change in haemoglobin mass was less than 30 g. and insignificant. The mean values at the 3 tests were 515 g., 560 g. and 610 g.

*Cell volume.* Three cases had final cell volumes lower than the initial volumes, in

TABLE III.

*Mean Variations in Blood Volume, Cell Volume and Haemoglobin Mass in 20 Pregnant Women and their Relation to Changes in Surface Area.*

| | Mean duration of pregnancy, weeks | | | | |
|---|---|---|---|---|---|
| | 12.4 | 24.2 | | 35.6 | |
| | | | Per cent change | | Per cent change |
| *Absolute mean values.* | | | | | |
| Surface area, sq. m. ... ... | 1.58 | 1.64 | 4 | 1.70 | 8 |
| Standard deviation ... | 0.10 | 0.10 | | 0.10 | |
| Blood volume, ml. ... ... | 4300 | 4900 | 15 | 5400 | 26 |
| Standard deviation ... | 400 | 650 | | 800 | |
| Haemoglobin, g. ... ... | 515 | 560 | 8 | 610 | 19 |
| Standard deviation ... | 65 | 95 | | 90 | |
| Cell volume, ml. ... ... | 1650 | 1800 | 8 | 1950 | 18 |
| Standard deviation ... | 200 | 350 | | 250 | |
| *Mean values per sq.m. surface area.* | | | | | |
| Blood volume, ml. ... ... | 2700 | 2975 | 10 | 3180 | 18 |
| Standard deviation ... | 210 | 325 | | 400 | |
| Haemoglobin, g. ... ... | 320 | 340 | 6 | 360 | 12 |
| Standard deviation ... | 45 | 45 | | 40 | |
| Cell volume, ml. ... ... | 1060 | 1100 | 4 | 1160 | 9 |
| Standard deviation ... | 125 | 160 | | 120 | |

(2) *The Blood Volume, Haemoglobin Mass and Cell Volume.*

(a) *Absolute amounts.*

The mean values and their standard deviations are shown in Table III.

2 cases there was no change. In the other 15 cases the cell volume increased by 100–800 ml. The mean values at the 3 tests were 1,650 ml., 1,800 ml. and 1,950 ml.

(b) *The levels of blood, haemoglobin and cells in the body.*

The variations in the absolute values are to some extent due to the different body sizes of the subjects. A more accurate comparison of the results is obtained if the blood volume, haemoglobin mass and cell volume per square metre of body surface are considered. The means for these values are also shown in Table III.

*Blood volume level.* The mean values at the first, second and third tests during pregnancy were 2,700 ml./sq.m., 2,975 ml./sq.m. and 3,180 ml./sq.m., compared with 2,660 ml./sq.m. for non-pregnant women. Although there was a considerable difference between the means at the 3 tests, in many cases the blood volume at the end of pregnancy was not outside the range of the values found in the non-pregnant women. This overlap is apparent from the standard deviations (Table III). The standard deviations also showed that the blood volume became more variable as pregnancy advanced. Thus the standard deviation from the mean for non-pregnant women was 163, for the first test in pregnancy it was 210, for the second 325 and for the third 400. From this it is apparent that in the later months of pregnancy the blood volume could not be predicted with any accuracy, even when account was taken of the body size.

There was no significant difference between the mean blood volume at the first test in pregnancy and the mean blood volume of non-pregnant women. This suggested that in the early months of pregnancy there was little change in the volume. A comparison of different groups of women when the numbers are so small is not, however, reliable. The alterations in blood volume in the early months are difficult to investigate as the value prior to pregnancy is not known. The postpartum value is probably the best available measure of the non-pregnant blood volume, if it is obtained several weeks after parturition, when any blood loss has been made good. Two women were investigated 5 weeks postpartum. The blood volume of the first was 2,650 ml./sq.m. postpartum and 2,850 ml./sq.m. when 8 weeks pregnant. This was a difference of 8 per cent. That of the second was 2,600 ml./sq.m. postpartum and 2,950 ml./sq.m. when 13 weeks pregnant. Here there was a difference of 13 per cent.

*Haemoglobin and cell levels.* The mean values for haemoglobin per square metre were 320 g., 340 g. and 360 g. at the 3 tests during pregnancy. The mean cell volumes per square metre were 1,060 ml., 1,100 ml. and 1,160 ml. at the 3 tests. The haemoglobin mass and cell volume did not show the increasing variability exhibited by the blood volume. This is shown by the fact that the standard deviations did not increase.

(c) *The increases in blood volume, haemoglobin mass and cell volume.*

The increases in haemoglobin mass and cell volume during pregnancy were proportionately less than the increase in blood volume. Thus when the values per square metre are considered it is seen that between the first and second tests during pregnancy the blood volume increased by 10 per cent, the haemoglobin mass by 6 per cent and the cell volume by 4 per cent, while between the first and third tests the blood volume increased by 18 per cent, the haemoglobin mass by 12 per cent and the cell volume by 9 per cent.

The significance of these increases was investigated statistically and the results are

shown in Table IV. Only 19 of the 20 cases were considered as the case with an initial hypochromic anaemia, who responded to iron medication with an increase of haemoglobin and cells, was excluded. It will be seen that the increase in blood volume was significant at both the second and third tests. The increase in haemoglobin mass and the increase in cell volume were only significant by the third test.

TABLE IV.

*The Increase in Blood, Cell and Haemoglobin Concentration in the Body During Pregnancy* (19 *cases*).

| Per sq. m. surface area | Initial values | Mean increase at Second test | | | Mean increase at Third test | | |
|---|---|---|---|---|---|---|---|
| | | | St.E. | t. | | St.E. | t. |
| Blood volume, ml. | 2700 | 280 | 80.65 | 3.47 | 475 | 94.60 | 5.02 |
| Cell volume, ml. | 1070 | 10 | 40.80 | 0.24 | 80 | 35.14 | 2.22 |
| Haemoglobin, g. | 323 | 14 | 11.47 | 1.19 | 29 | 10.20 | 2.84 |

The increase is significant when t is greater than 2.11.

(3) *The Relation of the Levels of Haemoglobin and Cells in the blood to their amounts in the Body.*

As pregnancy advanced the total amounts of haemoglobin and cells rose, but owing to the disproportionate increase in the total plasma the levels of haemoglobin and cells in the blood fell. The percentage haemoglobin and haemotocrit during pregnancy did not, therefore, bear the same relation to the total amounts of haemoglobin and cells as they had in non-pregnant women. If the increase in blood volume had been constant in amount in all pregnant women, it would have been possible to find, for the different stages of pregnancy, the blood levels which represented normal total amounts of haemoglobin and cells. Since, however, the increase in blood volume was very variable this was not possible. It was in fact found that, by the third trimester of pregnancy, there was little or no correlation between the levels of haemoglobin and cells in the blood and their total amounts. The correlation coefficient for haemoglobin was 0.145, standard error 0.233 and that for cells was 0.025, standard error 0.236. These figures may be compared with those for non-pregnant women. The correlation coefficient for haemoglobin was then 0.843, standard error 0.127, and that for cells 0.817, standard error 0.136. On the other hand it was apparent that the haemoglobin and cell levels in the blood by the third trimester of pregnancy were inversely correlated with the blood volume. The correlation coefficient of haemoglobin percentage on blood volume per square metre was −0.532, standard error 0.120, while that of haematocrit on blood volume per square metre was −0.560, standard error 0.130. Both these coefficients were significant, while the corresponding ones for non-pregnant women were not.

(4) *Two Cases Exhibiting Anaemia During Pregnancy.*

(*a*) *Hypochromic anaemia.*

This patient was one of those originally selected for investigation as a normal case. The values found during the first and second trimesters were similar to those found in other pregnant women. When the third test was carried out at the 36th week it was found that the haemoglobin had fallen from

80 per cent at the second test to 70 per cent. This value was not abnormally low for this stage of pregnancy, but when the blood volume was estimated it was found that this had fallen from 3,100 ml./sq.m. to 2,700 ml./sq.m., so that the haemoglobin mass was now only 260 g./sq.m. as compared with 350 g./sq.m. at the second test and the cell volume was only 900 ml./sq.m. as compared with 1,100 ml./sq.m. Thus while the blood haemoglobin level had decreased by 12 per cent, the total haemoglobin had decreased by 24 per cent. The cell volume had decreased by only 18 per cent, so that there was a fall in the colour index which was now 0.73.

(*b*) *Pernicious anaemia of pregnancy.*

This case was found to have a severe megalocytic anaemia when 29 weeks pregnant. Her blood haemoglobin level was 28 per cent, haematocrit 13 per cent and colour index 1.33. She had a blood volume of 3,000 ml./sq.m., which was normal for this stage of pregnancy, but a total haemoglobin mass of only 120 g./sq.m. and cell volume of 400 ml./sq.m. After 4 weeks treatment the blood haemoglobin level was 66 per cent, haematocrit 34 per cent and colour index 1.11. The blood volume had now fallen to 2,500 ml./sq.m. Since during the same time there had been a fall of 1.5 kg. in weight, owing to loss of oedema fluid, it seems that the original high blood volume may have been due to a hydraemia, not to a true pregnancy increase. The haemoglobin mass was now 230 g./sq.m. and the cell volume 850 ml./sq.m. After 8 weeks treatment the haemoglobin was 72 per cent, the haematocrit 36 per cent, and colour index 0.92. The blood volume had risen again, to 3,400 ml./sq.m. and the total haemoglobin and cell volumes were 340 g./sq.m. and 1,200 ml./sq.m., normal values for this stage of pregnancy. Between the second and the final estimations the blood haemoglobin level thus showed an increase of 9 per cent and the haematocrit an increase of 6 per cent. But since there had been a marked increase in the blood volume, the haemoglobin mass had increased by 48 per cent and the cell volume by 41 per cent.

## Conclusions and Discussion.

The changes which occurred in the peripheral blood of the 20 pregnant women investigated, were a fall in haemoglobin concentration, cell volume and cell count, which were parallel so that there was no appreciable change in the mean corpuscular haemoglobin content, colour index or mean cell volume, all of which remained within normal limits. These changes are similar to those found in previous complete blood examinations of normal pregnant women.[2a, 2b, 8, 9, 10, 11] Iron administration failed to raise the haemoglobin level unless the colour index was low. This also has been found previously.[10, 12]

The blood volume was found to increase throughout the course of pregnancy. The increase was more than could be accounted for by alterations in body size. The haemoglobin mass and cell volume also increased, but only slightly more than would be expected from the increase of body size. This might be accounted for by the vascularity of the new tissues formed. The mean values found for the blood volume during pregnancy agree well, when calculated as volume per square metre of body surface, with those recorded by Dieckmann and Wegner,[2] and Thomson *et al.*[3] The 3 sets of values are shown and compared in Fig. 1.

The total amount by which the blood volume rose during pregnancy was difficult to determine, since values before pregnancy were not available. Postpartum values were the only possible indication of the original blood volume. These were

obtained in two cases and were considerably lower than the values in the same women during the first trimester of pregnancy. Dieckmann and Wegner[2] and Thomson *et al.*[3] also found this. It would therefore appear that the increase in blood volume starts early in pregnancy and that the total rise is greater than that observed between the end of the first trimester and the last months.

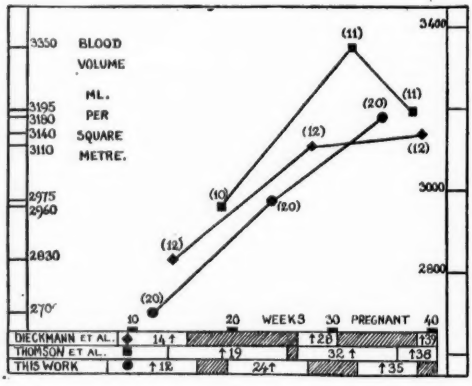


FIG. 1.

THE MEAN BLOOD VOLUME AT DIFFERENT STAGES OF PREGNANCY.

The blood volume is expressed as ml. of blood per square meter of body surface. The present results are compared with those of two previous studies. The numbers of cases in each group are shown in parenthesis and at the bottom of the figure are shown the periods during which each group was investigated and the mean time of investigation.

There were large variations in the amount of the increase in blood volume observed during pregnancy and no reason could be found for this. There was no correlation between the size of the increase and the age of the subjects, size of child and placenta, or with blood-pressure levels. This variability of the increase in blood volume was also noted by Dieckmann and Wegner.[2] The increases observed by Thomson *et al.*[3] were more constant.

The fall in the level of haemoglobin and cells in the blood during normal pregnancy was due to the fact that the plasma volume increased more than did the haemoglobin mass and cell volume. The small variations in the haemoglobin level in the blood, seen in the women in the third trimester, were due to variations in the blood volume, rather than to variations in the total haemoglobin.

In abnormal cases, however, a fall in haemoglobin level in the blood may be due to a decrease in the total haemoglobin. This was so in the two anaemic cases investigated. These cases also illustrated the difficulty of assessing the degree of anaemia in pregnancy from the blood haemoglobin level alone. The presence of anaemia was, however, apparent from further examination of the peripheral blood, the colour indices being in each case abnormal.

These findings may be employed to explain the changes in the haemoglobin level in the blood found in a larger series of women from the same antenatal clinic, who were investigated over the same period in 1944. The results of that investigation were recorded in our previous paper.[14] The haemoglobin level of the women fell steadily throughout pregnancy till the last weeks. It now appears that this fall was due to an increase in blood volume, the plasma increase being out of proportion to that of haemoglobin. In the last weeks the haemoglobin level rose in many of the women. No explanation of this terminal rise was obtained from the present results, but the rise was also found by Thomson *et al.*[3] who were able to correlate it with a fall in the plasma volume.

It was also found in the larger series that the blood haemoglobin level of the older women tended to fall more than did that of the younger ones. The 20 women, investi-

gated in detail, did not show any variation with age, but this is not surprising with such a small number. It seems probable that the variation in blood haemoglobin level with age, in the larger series, was due to variation in the plasma volume. The alternative explanation is that there was an increasing failure of haemoglobin formation with advancing years. This appears unlikely in view of the fact that the effect of age was apparent throughout the series, so that the levels were lower even in women of 25 than in those of 20, and it is difficult to believe that there can have been any failure of haemopoesis at such an early age. Fullerton,[13] who also observed lower haemoglobin levels in older women, considered that they were due to these women having started pregnancy at lower levels than the younger ones. This explanation is not supported by the present results, which showed that the difference was due to a more rapid fall during pregnancy and only became apparent in the later months.

Although in normal women the fall in haemoglobin level during pregnancy was due to dilution of the haemoglobin mass with plasma, a fall may also occur as a result of failure of haemoglobin formation. This was the case in the two anaemic cases investigated. In our previous paper[14] the haemoglobin levels of a series of pregnant women, seen in 1942, were reported. The levels were lower, all through pregnancy, than in 1944 and it is suggested that this was due to the combined effects of plasma dilution and deficient haemoglobin formation. This is supported by the fact that in 1942 the women who had been subjected to the strain of repeated pregnancies had lower haemoglobin levels than had the primiparae.

A satisfactory explanation of the increase in plasma volume during pregnancy has not yet been found. The present work did not provide any new evidence on the point, so nothing can be added to the adequate discussions of previous investigators.

## Summary.

1. The blood volume was estimated by the dye method (Evans blue) in 20 non-pregnant women and in 20 women 3 times during pregnancy. Various criticisms of the method, both general and as applied to pregnancy, were explored and found not to be applicable.

2. The blood volume in normal non-pregnant women was proportional to the body size, as measured by surface area, so that the concentrations of haemoglobin and cells in the blood were proportional to their concentrations in the body.

3. The blood volume increased during normal pregnancy. There was an increase of whole blood to supply the added maternal tissues, but there was also a further increase of plasma.

4. The disproportionate increase in plasma resulted in a fall of haemoglobin and cell concentration in the blood, but the normality of the low levels resulting was confirmed by the fact that the concentration of haemoglobin in the cells and the size of the cells remained within normal limits.

5. The amount of the increase in plasma during pregnancy was very variable and in this series by the later months of pregnancy the levels of haemoglobin and cells in the blood reflected inversely the blood volume, rather than the level of these substances in the body.

6. Two cases of anaemia occurring during pregnancy are reported, illustrating how the changes in blood volume obscured the changes occurring in the solid blood elements.

7. The findings were applied to explain

the changes in haemoglobin level found in two larger series of women and reported on in the previous paper.

We wish to express our thanks to Professor L. S. P. Davidson, at whose suggestion this work was undertaken, and to Professor R. W. Johnstone for allowing us to investigate his patients.

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# A Survey of the Relation Between Epilepsy and Pregnancy

BY

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ALTHOUGH the epileptic convulsion has been known to the medical world since ancient times, the elucidation of its cause and mode of production has not yet been fully achieved. Aetiological factors such as cerebral trauma and organic disease have been recognized for centuries, and fits so caused are designated by the term "symptomatic epilepsy." Probably in the future the origin of all fits will become known and all epileptic convulsions will then be included in this category, but at present there exists a large group apparently unrelated to any causal disease. These fits, which comprise the 2 forms of *grand mal* and *petit mal*, are usually regarded as cases of "essential epilepsy" or "idiopathic epilepsy." It is these idiopathic fits that will be dealt with here, and their manifestations as encountered in the obstetric patient will be portrayed and discussed.

## EPILEPSY IN OBSTETRIC LITERATURE.

It is agreed by almost all authorities that idiopathic epilepsy occurs in all races and has the same incidence in the 2 sexes. There are many statistics giving the ages of onset of fits, the most comprehensive being those of Turner.[1] In an analysis of 1,000 cases of epilepsy he showed that in 27.2 per cent fits began before the age of 9 years, in 55.7 per cent between 10 and 22, and in the remaining 17.1 per cent between 23 and 70 years. The average age of onset in males he found to be 13.7 and in females 15.5 years. He concluded that the age of 11 to 15 years was the most dangerous epoch, and this was so because of the influence of puberty. The frequency of fits is, of course, extremely variable from case to case, and is modified by the various drugs prescribed for their control, but is sometimes influenced by external factors. Thus, fits are said to occur less frequently in hot weather with the greatest incidence in May and October;[2] this seasonal influence was appreciated by Hippocrates who considered that they were most frequent in the spring. However, more apparent than these variations, are those which are known to be associated with menstruation. Thus, fits may occur only at the time of the period, either just before or during its course, but rarely just after it has ended; if they occur continuously, they may be more frequent at this time. This close association of menstruation with epilepsy was noted by Bachmann,[3] who stated that during temporary sterilization induced by exposure of the ovaries to X-ray irradiation, there was a corresponding cessation of the fits. Sometimes a different type of clinical picture is seen. Kinnier Wilson[2] described a patient who had a solitary fit at puberty which was not repeated until the time of the menopause, whilst similar cases recorded by Elliotson[4] and Binswanger[5] had epileptic fits regularly until the menarche, and then were free from them until the menopause. Perhaps more remarkable still was Filia's[6] case, in which

a breast-fed infant had convulsions only when its mother was menstruating. Kinnier Wilson[2] recorded the case of a girl who had *petit mal* only at the time of her mother's periods, although he was forced to the conclusion that this must have been a coincidence.

Following upon marriage there is usually no change in the frequency of the epileptic fits, although Sachs[7] and Muskens[8] each reported cases which did improve after marriage. Strong emotion is known to be a factor which causes fits, and so it is to be expected that fits might be induced by sexual intercourse, this was so in the case presently to be described, although no less an authority than Kinnier Wilson considers that convulsions are unrelated to coitus.

Most authorities are of the opinion that epilepsy does not lower fertility, although Essen-Möller[9] stated the contrary. Stander[10] in his textbook gives an incidence of 0.14 per cent of pregnancies complicated by epilepsy, whilst Baptisti[11] recorded 37 cases amongst 54,688 patients; an incidence of 0.067 per cent. In the Obstetric Unit of the West Middlesex County Hospital there have been 21 cases of idiopathic epilepsy in the last 7 years, during which time there have been 14,349 deliveries, i.e., an incidence of 0.146 per cent. This of course cannot be considered the true incidence in the general population, as only patients with an apparent or suspected abnormality are booked and admitted.

Most writers agree with Greenhill[12] that epilepsy usually has no effect on pregnancy. Thus Nerlinger[13] had only 3 cases of abortion in 153 epileptic pregnancies, and 2 cases of premature labour in 102 pregnancies. Cases of abortions and premature labours following fits have however been reported, the highest incidence being recorded by Waldstein[14] of 10 abortions and 4 premature labours occurring in 54 epileptic pregnancies.

When the effect of pregnancy on epilepsy is considered, a variable picture is seen in which the frequency of the fits may be either reduced or increased or may remain uninfluenced. Different writers have made widely different statements—thus Curschmann[15] considered that patients usually improved, Binswanger[5] that they usually became worse, and Baptisti[11] that they were usually unaffected. Amongst the worsened cases must be included those in which the convulsions may have been absent for years, only to be revived by the pregnancy. In Table I are given the statistics that are available on this point, together with those from the West Middlesex County Hospital.

TABLE I.
*The Incidence of Fits During Pregnancy.*

| Observer | Better Per cent | Worse Per cent | No Influence Per cent |
|---|---|---|---|
| Nerlinger[13] ... ... | 35.6 | 36.2 | 11.5 |
| Rubeska[16] ... ... | 33.3 | 33.3 | 33.3 |
| Baptisti[11] ... ... ... | 17.0 | 13.0 | 70.0 |
| Béraud[17] ... ... ... | 50.0 | — | — |
| Waldstein[14] ... ... | 50.0 | — | — |
| West Middlesex County Hospital ... ... | 5.5 | 42.0 | 52.5 |

It will be seen that there is no agreement amongst the authors. Probably Rubeska[16] is as near the truth as anybody when he considers that one third of the cases improve, one third become worse, and one third remain unchanged. Turner[1] found that in 7 of his 21 cases which were adversely affected the relapse was associated with quickening.

It might be thought that the cases which were subject to convulsions at the times of the menstrual periods would be amongst those who became worse during pregnancy. Nerlinger[13] showed that this was not so, as

some of his cases of menstrual epilepsy improved and others deteriorated during pregnancy. Baptisti[11] quoted 7 cases of menstrual epilepsy, 4 of whom improved during pregnancy whilst 3 remained unchanged. We must agree with Sachs[7] that when pregnancy occurs in an epileptic mother it has an influence on the disease which is completely unpredictable. The effect may, in fact, differ in successive pregnancies in the same patient; this occurred in a case of Turner's who was free from attacks in 1 pregnancy, but had them more frequently in the next. Of the improved cases all observers are agreed that the relief is not permanent—Döderlein[18] emphasized that epilepsy is never cured by pregnancy, although Muskens[8] described a patient subject to fits from the time of puberty in whom they ceased entirely after her last labour.

Numerous cases are on record in which convulsions first occur during pregnancy, and these are referred to as cases of "pregnancy epilepsy." Echeverria,[19] Gowers,[20] Bachmann,[3] and Struthers[21] all described cases of this type; sometimes the fits continue permanently after delivery, as in a case mentioned by Browne,[22] where the residual convulsions were usually of the menstrual type, and sometimes they recur only during subsequent pregnancies. Nerlinger[13] however denied that fits can begin during pregnancy, pointing out that there would not be an equal incidence in the sexes if pregnancy were an actual cause of the disease.

A relation between the incidence of fits and the sex of the child has often been suggested. Thus Pachelt,[23] Muskens[8] and de la Motte[24] all described patients who had repeated pregnancies during which epileptic fits occurred when the foetus was a male, but were absent when it was a female.

Labour itself may coincide with the onset of epileptic convulsions, which may continue thereafter with a varying frequency for many years. Turner[1] described 5 cases of this type and mentioned 17 in which delivery caused a relapse in apparently cured cases after a normal pregnancy. Hayden[25] recorded a multiparous epileptic who always had her most severe convulsions during the birth of each child.

The puerperal and lactational periods are also sometimes responsible for the onset of fits and for the relapse of an apparently cured case. Gowers[20] and Struthers[21] reported cases of puerperal epilepsy, and Turner[1] mentioned one in which fits began during lactation, ceased on weaning and only recurred during 3 successive lactational periods. Stander[10] considers that lactation may increase the frequency of attacks, whilst Greenhill[12] doubts if this is so and is of the opinion that the aggravation of epilepsy by suckling is merely a medical myth.

## Case Reports.

At the West Middlesex Hospital during the 7 years 1939–45 inclusive, there have occurred 21 deliveries in 18 epileptic mothers. Records of 19 of these pregnancies in 16 patients have been available for analysis and are presented in Table II, from which the following conclusions can be drawn.

*Family history.* It is remarkable that in only 1 case (Case 10) was there a family history of epilepsy. Apart from actual convulsions evidence of mental instability or defect could not be obtained in the patients' parents or siblings. None of the babies showed any evidence of inheriting the taint. The significance of these findings will be discussed later, when the problem of heredity is reviewed.

*Age of onset of fits.* It will be seen that

TABLE II.

*An analysis of 19 Pregnancies and Del in 16 epileptics.*

| Case No. | Age | Date of delivery | Family history of epilepsy | Age at Menarche | Age of onset of fits | Nature of fits | Total number of pregnancies | Intens fits du Pregn | idence clamp naemia |
|---|---|---|---|---|---|---|---|---|---|
| 1. | 42 | Jan. 1939 | — | 14 | 14 | Improved after marriage | 4 | Unaffe | eralize ema |
| 2. | 30 | July 1939 | — | 16 | 26 | — | 1 | Unaffe | ?. 170/ None |
| 3. | 32 | July 1939 | — | 15 | Not known | Menstrual | 4 | Unaffe | None |
| 4. | 38 | Oct. 1939 | — | 12 | Not known | Nocturnal | 5 | Worse | None |
| 5. | 28 | Apr. 1940 | — | 14 | 24 | Nocturnal | 2 | Worse | None |
| 6. | 37 | Oct. 1941 | — | 14 | 7 | — | 1 | Impro | None |
| 7. | 24<br>26<br>27 | June 1942<br>Feb. 1944<br>Nov. 1945 | — | 11 | 20 | — | 3 | Unaffe | ema o minur ?. 146/ oedem ?. 145/ None |
| 8. | 22 | Oct. 1942 | — | 13 | 2 | *Petit mal* | 1 | Unaffe | None |
| 9. | 28 | Dec. 1942 | — | 14 | 14 | Menstrual | 2 | Worse | None |
| 10. | 32 | Aug. 1943 | Mother has fits | 13 | 13 | Menstrual | 5 | Worse | eralize ema |
| 11. | 24 | Sept. 1943 | — | 11 | 24 | Gestational | 3 | Worse | ?. 140/ eralize ema |
| 12. | 38<br>40 | Mar. 1944<br>Aug. 1945 | — | 17 | 37 | Began in previous pregnancy | 11 | Worse<br>Unaffe | None None |
| 13. | 41 | Aug. 1944 | — | 17 | 15 | Menstrual | 2 | Worse | None |
| 14. | 39 | Sept. 1944 | Not known | Not known | 32 | — | 6 | Unaffe | None |
| 15. | 40 | Aug. 1945 | — | 14 | 26 | — | 4 | Worse | ?. 170/ 100/ eralize ema |
| 16. | 29 | Nov. 1945 | — | 12 | 19 | Nocturnal | 1 | Unaffe | None |

in only 4 of the 16 cases did the fits commence during the "dangerous epoch" between 11 and 15 years of age, although in 3 cases they began in the same year as menstruation, 2 of these being menstrual in type.

*Menstrual epilepsy.* Four cases of menstrual epilepsy were encountered, of which 3 became worse during pregnancy and 1 remained unaffected, thus differing markedly from Baptisti's 7 quoted cases.

*Gestational epilepsy.* The table contains 2 cases of gestational epilepsy, 1 which began in the pregnancy under review (Case 11), and 1 which began in a previous pregnancy (Case 12). In both cases the fits have so far continued since delivery and are not associated with menstruation.

*Behaviour of fits during pregnancy.* If the cases of gestational epilepsy be included, it will be seen that 8 cases became worse during pregnancy, 1 was improved

| idence of eclamptic xaemia | No. of fits during period of toxaemia | Labour and puerperium | Sex of child | Born alive or dead | Birth weight | Method of feeding |
|---|---|---|---|---|---|---|
| eralized ema P. 170/100 | 1 | Normal | Male | Alive | 7 lb. 8 oz. | Breast—4-hourly |
| None | — | Normal | Male | Alive | 6 lb. 7 oz. | Breast—3-hourly |
| None | — | Normal | Female | Alive | 5 lb. 13 oz. | Breast—3-hourly complemented |
| None | — | P.P.H. | Male | Alive | 8 lb. 11 oz. | Breast—4-hourly |
| None | — | Normal | Female | Alive | 7 lb. 9 oz. | Breast—4-hourly |
| None | — | Normal | Female | Alive | 6 lb. 1 oz. | Artificial |
| ema of legs minuria P. 146/90 | 2 | Normal | Female | Dead | 7 lb. 7 oz. | —— |
| oedema P. 145/90 | 1 | Normal | Male | Alive | 7 lb. 14 oz. | Breast—4-hourly |
| None | — | Normal | Male | Alive | 6 lb. 11 oz. | Breast—4-hourly |
| None | — | Normal | Female | Alive | 6 lb. 8 oz. | Artificial |
| None | — | Normal | Female | Alive | 5 lb. 10 oz. | Breast—3-hourly complemented |
| eralized ema P. 140/90 | Many | Normal | Male | Alive | 8 lb. 2 oz. | Breast—4-hourly |
| eralized ema | Many | Normal | Male | Alive | 7 lb. 0 oz. | Breast—4-hourly |
| None | — | Normal | Female | Alive | 7 lb. 14 oz. | Breast—4-hourly |
| None | — | Normal | Male | Alive | 7 lb. 10 oz. | Breast—4-hourly |
| None | — | Normal | Female | Alive | 8 lb. 0 oz. | Breast—4-hourly |
| None | — | Normal | Female | Alive | 6 lb. 4 oz. | Artificial |
| P. 170/200 100/120 eralized ema | Many | Normal | Male | Alive | 6 lb. 3 oz. | Breast—4-hourly |
| None | — | Normal | Male | Alive | 7 lb. 7 oz. | Artificial |

and 10 were unaffected. Reference to Table I will reveal that these figures do not agree even approximately with those of any previous observer. In the adversely affected cases, no association with quickening was noted.

There are 2 cases of repeated pregnancies. In case 7 (3 pregnancies) the fits were unaffected at any time by the gestation; in case 12 (2 reported pregnancies) the fits had begun in the 9th pregnancy, were intensified in the 10th, and unaffected in the 11th.

*Seasonal influence.* The time of the year of the pregnancy and labour bears no relation to the behaviour of the fits.

*Influence of pre-eclamptic toxaemia.* The presence or absence of pre-eclamptic toxaemia, as revealed by the existence of oedema, basic blood-pressure above 130/70 mm. Hg. or albuminuria, was noted in each case. In 6 cases one or more

of these signs was present, and in 13 they were all absent. Of the 6 toxaemic cases the fits in 3 became worse during pregnancy and in 3 they were unaffected, although in these latter cases 1 or 2 fits occurred during the actual period of the toxaemia, even though they had been absent for months previously; of the 13 non-toxaemic cases 5 became worse, 1 improved and 7 were unaffected. The significance of these findings will be discussed later.

*The effect of epilepsy on the pregnancy.* Premature interruption of pregnancy did not occur in this series. In the first pregnancy of Case 7, the patient fell during a fit 4 days before delivery at term, after which she did not feel foetal movements and foetal heart sounds could not be heard on admission to hospital. Labour ensued uneventfully with the foetus in the left occipito-anterior position, but a macerated stillbirth resulted. The placenta appeared to be normal in structure and attachment.

*Labour and puerperium.* Apart from Case 4 in which there was a postpartum haemorrhage of 35 ounces, the labour and puerperium were normal in each case. Fits did not occur during labour, and none began during the puerperium.

*The baby.* No premature baby was born in these cases, and all the infants were alive and healthy, with the one exception already mentioned (Case 7). Ten of the babies were males and 9 were females. Of the pregnancies with male foetuses, in 4 the fits were increased in number, and in 6 they were unaffected; in association with females 4 were worse, 1 was improved and 4 were unaffected. In the 2 cases of repeated pregnancies, in the first (Case 7) the foetal sex had no effect on the frequency of the fits as they were equally unaffected whether the foetus was male or female, and in the second (Case 12) the fits had begun in the previous pregnancy (the 9th) with male twins, were worse in the 10th with a female foetus, and unaffected in the 11th with a male. It is apparent that no relationship between the incidence of fits and the foetal sex can be discerned in this series of cases.

*Breast feeding.* There is no doubt that epileptic fits in the mother constitute a contra-indication to breast-feeding for fear of damage to the baby. In these cases we have been guided by social conditions. If a third capable person can always be present at feeding times we have permitted the baby to be put to the breast; when this is impossible artificial feeding has been substituted. It will be seen that breast-feeding was allowed in 14 of the 18 cases. It was found however that breast-fed babies tended to be sleepy if the mother were being given a sedative mixture containing bromides.

In none of the mothers was the epilepsy aggravated by lactation, thus corroborating Greenhill's opinion that the danger of lactation has been exaggerated. Epilepsy beginning during lactation has not been encountered here, although observations have been of necessity restricted to the first 2 months after delivery whilst the patient has still been attending the post-natal clinic.

## The Cause of the Convulsion During Pregnancy.

Since the mode of production of the idiopathic convulsion in the non-pregnant patient is unknown, we are obviously foredoomed to failure if we attempt to portray its mode of production in the pregnant, parturient or lactating patient. Yet to understand this matter fully we have to probe it to even greater depths than this, for we have to describe the mechanism whereby in some cases the frequency of fits increases during pregnancy, in others it diminishes, whilst in others it remains

unaffected. Any explanation we can offer must thus be an extremely labile one, and must encompass either of two changes in opposite directions, or else no change at all. Let us examine this problem in the shadow of these difficulties and attempt to find what factors induce or relieve fits in a confirmed epileptic, and see if the state of pregnancy in any way intensifies or annuls these mechanisms.

In such an attempt to correlate the state of being an epileptic with the state of being pregnant, a facile solution dependent on such factors as the age of the patient, the season of the year or the sex of the child will not be found. Data in Table II effectively dispose of a simple solution along these lines. The most likely clue here is the co-existence of pre-eclamptic toxaemia, which we will show later has a bearing on the occurrence of convulsions.

A step towards the solution of this problem has been taken since a deeper insight into the mechanism of epilepsy has been achieved through the medium of the electroencephalograph. This has shown that epileptic subjects have a distinctive pattern of cerebral waves called by Lennox, to whom we are most indebted for this knowledge, "cerebral dysrhythmia." He and his colleagues have shown[26] that cerebral dysrhythmia is present in all patients during the time of the epileptic seizure, and is also present in 90 per cent of epileptics between the seizures; they found it to be present in approximately 10 per cent of normal persons. Dysrhythmia is not peculiar to epilepsy but is present also in an undue proportion of individuals whose psychical processes are abnormal. Its presence is a familial trait, for if the relatives of an epileptic are subjected to electroencephalography it is found that about 60 per cent of them will show dysrhythmia. Lennox *et al.* investigated the parents of 88 epileptic families and found 91 per cent of them to be affected. It is evident then that individuals who have this dysrhythmia are potential epileptics, and that the presence of some exciting factor is required to give rise to an actual convulsion. Menstruation and pregnancy might well be such a factor. Gestational epilepsy would then be regarded as the culminating event when the strain of pregnancy is imposed on a susceptible, dysrhythmic individual.

Bachmann[3] in discussing this point states rather aptly that pregnancy is not in itself a cause but acts rather as a catalyst in producing fits in a susceptible person. This conception is illustrated by a case of symptomatic epilepsy described by Westphal,[27] in which the patient was known to have a cortical cyst; when she became pregnant the fits increased in intensity and frequency, through the catalytic action of the pregnancy. When the cyst was removed the fits ceased and the pregnancy continued uninterruptedly. In a similar manner the action of convulsant drugs[28] such as camphor compounds and creatin when applied to the cortex is well known. Under the catalysing influence of pregnancy the experimental animal becomes increasingly susceptible to the irritant effect of these drugs, and the fits are more readily induced by smaller dosages.

Bearing these facts in mind, let us consider in what manner the physiological changes accompanying pregnancy can intensify the process of epileptogenesis and cause an increase in the number of fits. With the exception of cases of gestational epilepsy, the patient will probably know of her affliction, and will be receiving treatment prior to pregnancy. The dose of her depressant will have been adjusted to reduce and keep the fits to a minimum. When she becomes pregnant she may suffer from vomiting or altered gastric acidity, in which case the dose of sedative taken and

absorbed may be reduced. Moreover her weight will increase, partly due to the products of conception and partly due to water retention; the effective dose of her sedative will now not exert the same controlling influence and her epilepsy will become worsened—apparently by the pregnancy. If bromides are being used as a depressant their efficacy will be impaired by the pregnancy, for as there is a retention of Cl ions in the tissues at this time,[29] the Br ions will be displaced, and their sedative action will be rendered less effective. These circumstances, however, can only play a minor rôle, for in such cases increased dosages would restore the patient to her level of normality, whereas in actual fact, it is usually found that she becomes worse in spite of an increased dosage of drugs.

Apart altogether from the question of drugs, water retention itself may have a further important influence, for it is well known to be conducive to fits, presumably through the medium of cerebral oedema. Thus the performance of encephalography in confirmed epileptics[2] has shown abnormal meningeal spaces over the frontal and parietal areas of the brain with dilated ventricles—a picture in brief of chronic waterlogging. Experimentally, Rowntree[30] produced fits by injecting large quantities of water into dogs. It is equally conceivable that the water retention of pregnancy might serve to increase the fits in a susceptible individual. The water-pitressin test performed in non-pregnant epileptic subjects, as described by many workers, is not without interest here. Blyth[31] gave his patients water to drink over a period of 48 hours until their body weight was increased by 2 per cent. They were then given 300 c.cm. of water and $\frac{1}{2}$ c.cm. pitressin every 2 hours for 10 doses, and 45 fits were thereby induced in 49 suspect epileptics, of whom 39 (86.6 per cent) were verified later. Garland *et al.*[32] using a similar technique increased the body weight by 3.5 per cent and then found that injections of pitressin produced fits in 17 of 44 epileptics (39 per cent), in 12 of 32 doubtful cases (38 per cent), and in none of 20 controls. It is tempting to conclude that the state of pregnancy parallels this test, for although there is no proved increased secretion of pitressin at this time, the water retention causes an increase in body weight of over 3.5 per cent, so that the epileptogenetic mechanism may become operative. It is interesting to note that on averaging the results of many performances of this test, fits were induced in about one third of the total number of epileptics investigated—approximately the same proportion of epileptics that become worse during pregnancy. Possibly menstrual epilepsy can also be correlated with the water retention that is known to occur before and during the time of the menstrual period.

It has been shown that brain activity is dependent on the $CO_2$ tension in the blood.[33] Thus if dysrhythmia is produced in electroencephalographic tracings by anoxaemia, the addition of $CO_2$ will immediately restore the rhythm to normal. Moreover, deprivation of $CO_2$ will induce fits in epileptics; thus Janz[34] was able to produce fits in 10 per cent of epileptics by hyperventilation with subsequent lowering of the $CO_2$ tension in the alveolar air and blood. Venepuncture of the internal jugular has shown that the cerebral blood in patients subject to *petit mal* contains less $CO_2$ than in normal subjects. Now in pregnancy Porges and Novak[35] have shown that the $CO_2$ tension is reduced in the alveolar air, whilst the alkali reserve of the blood is reduced from 65 vol. per cent to 45 vol. per cent at term. This reduction in $CO_2$ may well be an exciting factor in causing an increase in the number of fits during pregnancy. A true alkalosis is known to be another aggravat-

ing factor in epilepsy, but this cannot play a part during pregnancy as the $p$H of the blood remains remarkably constant at 7.40.

Tauberhaus and Engle[36] have demonstrated that idiopathic epilepsy is sometimes associated with hypocalcaemia. Although the blood and cerebro-spinal calcium of epileptics are within normal range, a slight diminution may act as a trigger which fires off a convulsion. Now in pregnancy there tends to be a slight lowering of the level of calcium in the blood to an average of 9.5 mg. per 100 c.cm. at term.[37] This again may well be a worsening factor when pregnancy occurs in an epileptic subject.

Lastly, we must mention hormonal causes. Little can be said about them at present because the influence of the sex hormones on fits has not been adequately investigated, but the possible effect of their increased concentrations before menstruation and during pregnancy, as well as the reputed link between fits and the foetal sex, must be borne in mind.

Thus there are many channels through which the adverse strain of pregnancy may affect the susceptible individual—through water retention, $CO_2$ deficiency, hypocalcaemia and possibly altered hormonal relationships.

Let us now consider the opposite picture and see if there are any happenings in pregnancy which would tend to mitigate the severity of the convulsions. Bachmann[3] suggests that improvement may occur in pregnant women who were previously subject to menstrual epilepsy because the causal factors are no longer present when amenorrhoea of pregnancy exists. However he gives no explanation of the mechanism whereby this improvement is effected. A decreased number of fits is known to result in confirmed epileptics from the development of acidosis.[2] Thus fasting and a ketogenic diet both reduce the number of fits in epileptics, and have indeed been employed as therapeutic measures. It is possible therefore that excessive vomiting occurring in pregnancy may induce a state of ketosis which exerts a beneficial effect on the disease. It might be argued that as the ketosis is only of short duration it cannot lessen the fits throughout the whole course of pregnancy; this however is not necessarily so, for it is known that in epileptics any event which reduces the fits may have a prolonged beneficial effect. Thus scarlet fever, measles and varicella have all caused a cessation of fits long after the period of infection is over, whilst Gowers[20] reported a case of typhoid fever occurring in an epileptic boy after which fits remained absent for 20 years. Garrod[38] described an epileptic patient in whom the fits were permanently cured by an attack of gout. In a similar manner it is reasonable to conclude that ketosis occurring in early pregnancy may reduce the number of fits throughout its whole duration.

One other observation deserves mention. Altenburger and Stern[39] found that there is an underfunctioning of the posterior lobe of the pituitary gland in epileptics which may play a part in causing fits; the guinea-pig uterus suspended in epileptic serum does not undergo rhythmic contractions as it does in the serum of healthy controls. Possible alterations in the posterior pituitary during pregnancy might eliminate this causal process so that the patient shows some improvement.

Study of the pregnant epileptic patient would be incomplete without consideration of electroencephalographic tracings taken during pregnancy. These do not appear as yet to have been investigated in the epileptic subject, but Gibbs and Reid[40] have taken tracings during normal pregnancy. They found that only 60 per cent of 20 pregnant women had a normal rhythm, compared

with 85 per cent of 100 normal non-pregnant controls. These figures are too small to base conclusions on, but they do suggest that pregnancy itself has not a beneficial effect on cortical activity, and that it would therefore tend to encourage rather than inhibit the occurrence of fits.

Summing this matter up, what are we to make of it? Probably all the factors mentioned play a rôle at some time in the genesis of fits; according to the different clinical course of each pregnancy, so will the water retention, the $CO_2$ deficiency, the hypocalcaemia or the ketosis play a dominant part, and so accordingly will the fits become worse, better, or remain unaltered. The alternating behaviour of the same patient in successive pregnancies will be explained by the different clinical picture which characterises each pregnancy, and which may, by coincidence, correspond with a particular sex of the foetus. When an epileptic becomes pregnant, therefore, the course of her epilepsy will be dependent upon the course of her pregnancy, and the number of fits will result from the summation of related and antagonistic factors exercised on the nervous system of a susceptible and dysrhythmic individual.

## The Relation of Epilepsy to Eclampsia.

In view of the identical nature of the convulsion in epilepsy and eclampsia, it is not surprising that a relationship between the two diseases should have been postulated; if the convulsion is the same, may not the cause be so? At the close of the last century, Féré[41] suggested that eclampsia was an acute form of epilepsy, whilst Poten[42] considered them to be identical diseases. Zangemeister[43] partially inclined towards this view, stating that 2 per cent of eclamptics were left with residual epilepsy, and Féré agreed that epilepsy might be inaugurated by an attack of eclampsia. Cases have been reported which lend support to this hypothesis; thus Whapham and Hogg[44] described a patient who was delivered following a medical induction for severe pre-eclampsia, and who was discharged home on her 14th day, free from all signs of the disease. On the 17th day postpartum she had a typical convulsion. Rosenbaum and Maltby[45] recorded a case of persistent *petit mal* following eclampsia, and others have been quoted by Dexter and Weiss[46] and DeLee.[47]

A further connection between the two diseases is evident from the fact that a large proportion of the relatives of eclamptics are subject to convulsions, thus showing a constitutional predisposition to fits in these cases. Rosenbaum and Maltby[45] studied a series of 20 eclamptics and found that 12 gave a family history of convulsions—8 had relatives who were subject to epilepsy and 4 who had had eclampsia. A control series of 20 non-convulsive pre-eclamptics yielded only 2 cases with similar family histories. Though these cases are few in number, there is at least the likelihood that eclampsia occurs more readily in patients with a constitutional predisposition to convulsions.

One further point of interest is that eclampsia is known to occur more readily in some patients than in others. In 1893 Dührssen[48] stated that eclampsia occurred in two forms, *eclampsia reflectoria* characterized by cerebral instability and little evidence of liver or kidney disease, and *eclampsia toxica* distinguished by marked toxaemic changes in these organs. More recently Browne[22] has pointed out that with identical degrees of albuminuria, elevation of blood-pressure and other signs of toxaemia, one patient will go into eclamptic convulsions whilst another will not. It seems, therefore, that a varying degree of nervous instability exists which plays a part in causing the eclamptic fit.

Thus we are presented with 3 phenomena which call for correlation:

1. The occasional inauguration of epilepsy by an attack of eclampsia.

2. A predisposition to fits in the relatives of eclamptics.

3. The unequal tendency to fits in pre-eclamptics of equal severity.

The correlating factor in question appears to be the existence, in varying degrees in different patients, of the basic nervous instability which is revealed in electroencephalographic tracings as cerebral dysrhythmia. Epileptics and their relatives are not alone in being subject to this abnormality, for eclamptic patients are similarly afflicted, although not to the same extent. Thus Rosenbaum and Maltby[45] demonstrated the presence of dysrhythmia in 13 out of the 20 eclamptics (65 per cent) already quoted, as against only 2 of the 20 (10 per cent) non-convulsive pre-eclamptic controls. It is thus probable that when pre-eclamptic toxaemia supervenes in a patient with dysrhythmia it gives rise to eclampsia reflectoria, and in a patient free from this abnormality to eclampsia toxica. Similarly, when a patient has a certain degree of toxaemia, fits will supervene sooner if she has dysrhythmia than if she possesses a normal cerebral pattern. Again, as dysrhythmia is a familial trait, the incidence of fits—either epileptic or eclamptic—will be greater in the relatives of eclamptics than in normal subjects.

It is thus evident that the dysrhythmia is the connecting link between the two diseases, which is activated in each malady by an appropriate trigger mechanism to produce the convulsion. In eclampsia the cerebral vaso-constriction with or without oedema, culminating in cerebral anaemia, serves to fire off a convulsion, whilst in epilepsy the exciting mechanism is associated with cerebral oedema, hypocalcaemia, $CO_2$ deficiency or alkalosis.

Rosenbaum and Maltby conclude from their studies that the cerebral dysrhythmia is identical in these two conditions and that any person predisposed to fits (as revealed by dysrhythmia or by a family or personal history of convulsive disorders) is likely to exhibit them in the presence of pre-eclamptic toxaemia. Such cases they consider would not be true eclampsia, but rather "epileptic convulsions associated with toxaemia." This conclusion is borne out by the present study, provided the toxaemic cases develop some degree of cerebral oedema, for it is when generalized oedema occurs that the fits are produced. Thus of the 6 toxaemic cases portrayed, 3 had an increased number of epileptic fits during pregnancy, and although the remaining 3 were unaffected throughout pregnancy as a whole, they each had fits during the period of the toxaemia. The occurrence of these fits was found clinically to be associated with the onset of generalized oedema and was unrelated to the development of hypertension.

It is true that 5 of the 13 non-toxaemic cases became worse in the absence of generalized oedema; presumably one of the other suggested trigger mechanisms was the responsible factor in these cases.

In each disease then, there exists a common basic instability which is reacted upon by an exciting factor to produce a fit. The problem of the actual cause of the fit may not be resolved by such a simple equation as "basic instability *plus* exciting factor produces a convulsion" as Rosenbaum and Maltby suggest. It is true so long as oedema is the exciting factor, but otherwise the basic instability of each disease requires its own special trigger mechanisms to produce fits. Thus the epileptic instability is not influenced by physical stimulation or by high blood-

pressure, which are the eclamptic trigger mechanisms, to give rise to fits; similarly eclamptic instability is not influenced by the epileptic excitants to produce true eclampsia, for this did not supervene in any of the 6 toxaemic cases, which all tended on the contrary to run a mild course. The one factor which can play the dual rôle of excitant in both diseases is a generalized oedema particularly affecting the central nervous system; apart from this, the exciting factors are not interchangeable.

If fits were to supervene in the presence of severe pre-eclampsia it would be difficult to decide whether they were epileptic fits in a pre-eclamptic or eclamptic fits in an epileptic; in such a borderline case there would be real confusion, and status epilepticus in a toxaemic patient would closely simulate true eclampsia in an epileptic. We can draw the practical conclusion from these facts that toxaemia occurring in an epileptic subject calls for strict and early treatment, and measures must be directed particularly towards preventing the onset, or reducing the extent, of a generalized oedema.

## Status Epilepticus.

The occurrence of status epilepticus is a complication always to be most dreaded. It may supervene during pregnancy, labour (Turner[1]), or the puerperium (Struthers[21]); it may be preceded by worsening of the fits, or it may be the start of the whole epileptic process (Turner[1]). Sachs[7] reported 2 cases occurring in sisters, in both of whom it proved fatal. This result is the usual one met with when status epilepticus supervenes during pregnancy or labour; this fact has been emphasized by DeLee,[47] and Greenhill,[12] and Sachs went so far as to state that a fatal termination was inevitable. The only hope of saving the patient lies in terminating the pregnancy, and yet when this was done by manual dilatation of the os (Jardine[49]), or by manual dilatation and packing the uterus (Sachs[7]), the result was still a fatality. Nerlinger,[13] Neu[50] and Zweifel[51] all agreed that death nearly always occurred in spite of termination of the pregnancy. Termination was, however, recommended by Bachmann,[3] who stated that an immediate improvement sets in following the operation. It would appear on *a priori* reasoning that since the pregnancy itself, or one of its associated factors, is responsible for the development of the status, termination is logically indicated, provided this can be done in a manner calculated not to cause trauma or shock in a patient already seriously ill and in coma. As early observers found to their cost, accouchement forcé plays no more part in the treatment of pregnancy and the status epilepticus than it does in the treatment of the status eclampticus. With these considerations in mind, termination was carried out in a case of status epilepticus at the West Middlesex County Hospital, as will now be described.

## Case Report.

Mrs. V. I., a primigravida, aged 34, attended the antenatal clinic on October 5th, 1945, when she was 3 months pregnant.

*Personal history.* She had scarlet fever at the age of 10 years without residual nephritis. The menarche also occurred at 10, cycle 7/21, regular and painless. At 16 years of age fits in the form of *grand mal* had begun. There was no family history of epilepsy. The fits were induced by menstruation, over-eating, constipation, excitement and depression. Their frequency was kept in check by luminal, but even large doses did not inhibit those occurring during menstruation. She was married when aged 24 years, and the fits then became worse; they occurred 4 times per week, were induced by sexual intercourse and were relatively unaffected by drugs.

*History of pregnancy* After 10 years of married

life, during which contraceptives were used, she became pregnant, and expected to be delivered on April 8th, 1946. During pregnancy the fits became worse in spite of increased dosages of drugs, sometimes occurring every night. When first seen at the antenatal clinic she was found to be 14 weeks pregnant, she had had no vomiting, but occasional headaches. All systems were normal on examination, and the Wassermann reaction was negative. Her blood-pressure was 120/74 mm. Hg. and her urine was normal.

Apart from the fits the pregnancy progressed normally until the 28th week, when on December 25th, 1945, she bled vaginally for 1 hour. She reported this at her next visit to the clinic on January 1st, 1946, and was admitted forthwith. She had slight oedema of the ankles at this time, but this rapidly cleared with rest in bed, and her blood-pressure never exceeded 128/84 mm. Hg. She did not have fits during January, and further bleeding did not occur; blood group A; Hb. 76 per cent; and on inspection the cervix appeared healthy. She was kept on luminal gr. i nocte.

On February 4th, when 33 weeks pregnant, she became restless in her sleep and potassium bromide gr. 20 was given thrice daily in addition to the luminal. Slight oedema was now noticed in her ankles and hands; blood-pressure 110/70; urine normal.

On February 5th 2 major epileptic fits occurred. Blood-pressure 115/80. The luminal was increased to gr. 1½ t.d.s. and epanutin gr. 1½ t.d.s. was also given.

At 1.10 a.m. on February 6th she lapsed into status epilepticus and had 12 fits before 4.15 a.m., being unconscious and incontinent between them. She was given soluble luminal gr. 3 intravenously, and 16 c.cm. of paraldehyde intramuscularly, which produced a temporary cessation of the convulsions. She was then unconscious, with a pulse-rate of 140, a respiratory rate of 40, and a blood-pressure of 105/60. During the afternoon 8 further fits occurred, but ceased following pentothal 0.5 g. given intravenously, and the withdrawal of 30 c.cm. of cerebro-spinal fluid by lumbar puncture. This fluid was under the pressure of 10 to 11 cm. of water and was clear, containing 2 lymphocytes per c.mm., glucose 100 mg., chlorides 760 mg., total proteins 40 mg., without increase in globulins, per 100 c.cm. Her condition was then slightly improved, temperature 100°F., pulse 130, respirations 30. The condition of the foetus appeared satisfactory, the heart rate was constant at 150, and it presented by the vertex in the right occipito-lateral position.

The fits were now kept under control by pentothal 0.5 g. 12-hourly, supplemented with potassium bromide gr. 20 and luminal gr. ½, 4-hourly, and epanutin gr. 1½ 6-hourly. She remained unconscious and incontinent, but was able to swallow glucose drinks.

At 2 p.m. on February 7th it was decided to terminate the pregnancy by low rupture of the membranes. Accordingly, under pentothal 0.45 g. the membranes were stripped from the lower uterine segment and then ruptured.

*History of labour.* On February 8th the patient appeared improved, regaining consciousness but speaking with difficulty. Temperature 100.2°F., pulse-rate 104, respirations 28, and blood-pressure 120/70. Urine contained sugar and a trace of acetone. The slight oedema still persisted. Uterine contractions were present and labour was judged to have begun, but she did not complain of pains.

She remained in this condition throughout February 9th, during which day she had 7 fits, On February 10th she relapsed into unconsciousness and had her worst day—119 fits occurred in all, 67 of them being severe convulsions. By the evening her temperature, pulse-rate and respirations had risen to 103.8°F., 120, and 38 respectively; blood-pressure was 120/70 and she had developed oedema of the lungs. She was given a total of 1.75 g. pentothal and gr. ½ nembutal intravenously during the day, in addition to the potassium bromide, chloral, luminal and epanutin.

On February 11th the fits continued, and uterine contractions were felt to be stronger. Vaginal examination at 10 a.m. revealed the os to be fully dilated, with the vertex presenting. A forceps extraction was performed under pentothal 0.45 g. at 10.30 a.m., and a living male child, weighing 3 pounds 14 ounces, was extracted following episiotomy. The placenta, which appeared quite normal, followed 10 minutes later with the loss of 7 ounces of blood.

*History of puerperium.* Throughout the day of delivery she remained very ill, and had 6 more fits. On the following day she had 3 fits, but these

were the last, making a total number of convulsions of 163. Thereafter she improved slowly but steadily. She regained consciousness on this day, but was drowsy and talked slowly until February 18th. Her sedatives were discontinued except for luminal gr. i., t.d.s. The oedema was noticeably less on February 14th, and was completely gone by February 18th.

She had, however, some further trials to undergo. For the first few days after delivery she had marked pulmonary oedema, temperature 104°F., pulse-rate 120, respirations 40. This was considered to be due to bronchopneumonia, although physical signs of consolidation were not detected in the lungs. Her condition rapidly improved with sulphathiazole 24 g. and 600,000 units of penicillin given over 5 days.

Obstetrically the puerperium was normal until on February 27th she developed a *Bact. coli* urinary infection. A course of sulphathiazole was recommenced on March 1st, when she showed a marked sulphonamide-sensitivity reaction, her temperature rising to 105°F., and her skin developing a generalized maculo-popular rash. These quickly subsided when the sulphathiazole was stopped.

*The baby*. The baby was asphyxiated at birth, but responded to treatment. It lived only for 9½ hours, and during this time it had twitches and convulsions. At post-mortem examination a tear at the anterior end of the straight sinus was found with extensive haemorrhage between the hemispheres above the corpus callosum, on the tentorium, beneath the cerebellum and in the foramen magnum.

*Post-natal examinations*. Prior to discharge on March 18th, the patient was quite free from fits and was taking luminal gr. i, b.d. Blood-pressure 128/72, urine normal, there was no oedema, and her breasts and genitalia had involuted well.

When seen 1 month later she was still in good health and had not had further fits; 2 months afterwards the fits were recurring with their normal pre-gestational frequency.

## Discussion.

There are many features of interest in this case. From the age of 16 the patient had epilepsy of the menstrual type, the onset of which had post-dated the menarche by 6 years. Following marriage it had worsened, and this tendency had been aggravated by the pregnancy. During her month's rest in Hospital—necessitated by ante-partum haemorrhage for which a cause could not be determined—the fits ceased, and yet following the appearance of oedema in the hands and feet (unaccompanied by other evidence of pre-eclamptic toxaemia) the fits recurred and status epilepticus supervened quite rapidly.

There is no doubt that the termination of the pregnancy was responsible for saving the life of this patient. As the status followed upon the appearance of the oedema, it is probable that the diminution of oedema after delivery was the mechanism whereby the improvement was effected; it is true that oedema persisted for some days after the fits had ceased, but during this time it was steadily decreasing. After the inception of the status the patient was never at any time fit for Caesarean section or any major operative procedure; separation and low rupture of the membranes were judged to be the correct treatment in her case. It was unfortunate that 4 days elapsed before true labour pains started; during this time she must have prejudiced her chances of recovery by having 131 convulsions, which reduced her condition to the grave and almost moribund state which it reached just before delivery. Of all the sedatives employed, intravenous pentothal was the most efficacious. The treatment to be recommended for status epilepticus during pregnancy would therefore appear to be:

1. Surgical induction of labour by a non-shocking technique, such as separation and low rupture of the membranes.

2. Control of fits by pentothal and other sedatives, combined with judicious use of lumbar puncture, until delivery is accomplished and the fits have lessened or ceased.

3. Maintenance of cardiac strength by glucose fluids, oxygen, cardiac stimulants and skilled nursing.

4. Ready recourse to sulphonamides and penicillin to eliminate septic processes, such as bronchopneumonia, which are very liable to follow a period of coma and multiple fits.

With the recent popularisation of curare, the question of its use in the treatment of status epilepticus becomes of great interest. Theoretically through its mode of action by inhibiting the effect of acetylcholine on the myoneural junction it would seem to be the drug most likely to bring the convulsions under control. Bennett[52] described the use of curare in one case of status epilepticus (not associated with pregnancy) in which the seizures had been uncontrolled by sedatives and ether anaesthesia for 10 days; with continuous intravenous curare the patient was completely relaxed and free of seizures. Unfortunately death occurred from heart failure. It is possible that curare may be destined for a prominent rôle in the future treatment of status epilepticus, and its use should certainly be contemplated if the fits cannot be brought under control by other means.

## Sterilization.

Bachmann[3] considered that any pregnant patient who developed status epilepticus and recovered should subsequently be sterilized. He offered no evidence in support of this contention, and in view of the rarity of recovery it is not surprising that records of subsequent pregnancies after status epilepticus cannot be discovered. We do know that what happens during one pregnancy in an epileptic is no guide to what will happen in a subsequent pregnancy. However, the risk of a second visitation of the status is one which no patient should be allowed to run, and in these cases sterilization is certainly justified. In the case described this operation has been done.

Bachmann also advocated sterilization on eugenic grounds in other types of cases, for example, in all serious cases of epilepsy, cases of psychological disturbance and cases of cerebral degeneration. Greenhill[12] recommended sterilization in any epileptic patient whose condition was aggravated by pregnancy. Williams[53] advised it if the mentality progressively deteriorated with each succeeding pregnancy. Here these observers are on much less secure ground, and postulate controversial matter which does not concern us primarily as obstetricians. Even a severe case of epilepsy may undergo improvement during pregnancy, and if aggravated during one pregnancy it may be improved during the next, so that interference cannot be automatically warranted. Should the fits become worse during pregnancy, can we terminate and sterilize in anticipation of status epilepticus, as advocated by Binswanger[5] and Nerlinger?[13] It is doubtful if even this is justifiable for we have seen that although approximately one third of all epileptics become worse during pregnancy, the grand climax of status epilepticus supervenes very rarely, and would not warrant the sacrifice of these infants. It is claimed by Gibbs[54] that the occurrence of *grand mal* seizures can be predicted by accurate interpretation of electroencephalographic tracings. If an increased incidence of fits and the possible supervention of status epilepticus can be foretold in this way, a definite indication for interference would be presented, but patients subject to such electroencephalographic control must for a while remain very few. For the present, therefore, unless there are special indications advocated by the physician, sterilization must be restricted to those cases which have been rescued from status epilepticus.

## Heredity.

There remains to be said one final word about the infants of these epileptic mothers. Are they worth saving? As might be expected this is again a controversial point. Echeverria[55] in 1880 published the case histories of 553 children of 136 epileptics, and showed that 35 per cent died of fits during childhood, 18 per cent were mentally defective and only 19 per cent were normal. Casavieilt and Bouchet[56] quoted 58 children of 14 epileptic mothers of whom 37 per cent "died young" and only 24 per cent were healthy. These are grave figures indeed, but more recent observers suggest that they are unnecessarily so, as they probably include cases of congenital syphilis and other organic diseases. In 1916 Thom[57] investigated 553 children of 138 epileptics and found that only 10 (1.8 per cent) were subject to fits; Pilcz[58] studied 161 children of 144 epileptics and found only 3 (1.9 per cent) were affected. The concensus of opinion at a British Medical Association meeting held in Victoria in 1927 was that the frequency and importance of heredity had been exaggerated; Baptisti[11] agreed with this, stating that transmission occurred less often than was commonly thought. Stander[10] also found a family history of the disease in only 6 of 37 pregnant epileptics, whilst Myerson[59] investigated the relatives of 1,500 epileptics and found only 4 families to be affected, comprising 11 individuals in all. Russell Brain[60] summarises the problem by estimating that the risk of transmitting epilepsy is 1 in 10, and that in a family of 10 children the first is the one most likely to be affected. The absence of a family history of epilepsy in the cases presented from the West Middlesex County Hospital during the last 7 years certainly tends to confirm this latter view and probably the outlook for the child can be considered to be fairly good.

These opinions are supported by electroencephalographic studies which have shown that it is not manifest epilepsy which is inherited, but only the predisposition thereto, which is revealed by the presence of dysrhythmia. Lennox, Gibbs and Gibbs,[61] studying 183 relatives of 94 patients with epilepsy, found that 60 per cent had dysrhythmia, although only 2.4 per cent suffered from fits. They found dysrhythmia more frequently in female relatives and in the relatives of female patients and concluded that females have more predisposition to idiopathic epilepsy than is the case with males. They calculated on the above figures that manifest epilepsy occurs in every 25th dysrhythmic patient, and that the disease is more likely to be inherited if both parents are subject to dysrhythmia. Hence if an epileptic wife wishes to know the calibre of her future progeny, we can reassure her that the chance of a normal child is good, especially if the electroencephalographic tracings of her husband show a normal pattern.

Thus the statistics of recent observers and the results of electrical tracings combine with clinical experience to suggest that the inheritance of epilepsy is an infrequent occurrence; we can conclude accordingly that eugenic grounds offer no real indication either for the termination of an established pregnancy or for sterilization.

## Summary.

1. The literature of epilepsy complicating pregnancy, labour, the puerperium and lactation is reviewed.

2. Nineteen cases of epilepsy occurring in 16 mothers from 1939 to 1945 at the West Middlesex County Hospital are presented and discussed.

3. Factors influencing the behaviour of fits during pregnancy are postulated, with

special reference to the relation between epilepsy and eclampsia.

4. A case of status epilepticus occurring during pregnancy is presented, and termination of pregnancy, which was successful in this case, is advocated as the treatment of choice.

5. The modern outlook on sterilization and the transmission of epilepsy is reviewed.

ACKNOWLEDGMENTS.

I wish to express my appreciation to my colleagues throughout the hospital for their assistance in treating the case described; also to the Maternity Nursing Staff for their help, which was invaluable. My thanks also must be extended to Miss Gutman for the translation of foreign works.

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# Myasthenia Gravis and Pregnancy
*(A Case Report)*

BY

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IN a recent communication to this Journal, Wilson and Barr[1] drew attention to the fact that myasthenia gravis as a complication of pregnancy and the puerperium had received very little attention in the English medical literature. This fact becomes more significant in view of the improved prognosis for this disease since prostigmin became available in 1935. It would appear[2, 3, 4] that obstetrical opinion is slowly but definitely changing in regard to the management of these cases, and further evidence of the essential "normality" of pregnancy and labour in the prostigmin-controlled patient may therefore be timely.

Whilst it is agreed[5] that therapeutic abortion no longer has any place in the control of myasthenia gravis when complicated by pregnancy, there is less uniformity on the question of whether the patient should be allowed to deliver herself by the natural channels. "Of the few reported cases that have been delivered normally," wrote Wilson and Barr[1] in their extensive review of the literature, "the rapidity of labour and the absence of complications have been especially noted."

The case record to be submitted offers evidence in support of these observations.

## CASE RECORD.

Mrs. M. B. was an intelligent country girl who previously had always enjoyed good health. She was 25 years of age and recently married, when in June 1944 she began to notice weakness in her hands and legs. She experienced difficulty in manipulating small objects and suffered severe and frequent headaches. By March 1945 she was largely incapacitated; in her own words, "she felt useless." She was no longer able to carry out the simplest household duties, kitchen utensils were dropped and she felt constantly fatigued. Difficulty in swallowing had reached a stage where liquids regurgitated through the nose and semi-solid food only could be taken.

Breathing seemed to be a constant effort; the eyelids dropped, almost completely limiting her vision; she found that she could no longer smile, her face "seemed stiff." Talking became a great effort and her words would trail off and become indistinguishable. Sometimes when she tried to say something no sound would be produced. Her chin would drop on to her chest so frequently that she developed a troublesome ache across the back of her neck. Some of these symptoms could be temporarily relieved by rest, but the amelioration of symptoms seldom lasted for more than half an hour. There was, however, an appreciable variation in the severity of her condition from week to week and she particularly noticed an association with her menstrual cycle.

There was a definite remission of symptoms from approximately the 8th to the 23rd day of the intermenstrual period, followed by a relapse usually commencing about a week before the onset of menstruation and continuing throughout the period of the flow and for some days afterwards. Because of this association and because she realized that she was getting worse, the patient and

her husband developed the idea that pregnancy might be desirable as affording the means of securing a prolonged remission of the more severe symptoms. Contraception was therefore abandoned at this stage and menstruation ceased 3 months later; the last menstrual period commencing on 16th June, 1945. During these three months she had continued to lose weight; from 11 stone 5 lbs prior to her illness to 9 stone. She was constantly hungry, but because of her dysphagia was seldom able to satisfy her hunger. She found that she had become emotionally unstable and was inclined to cry on the slightest provocation.

During the first 3 months of her pregnancy there was an increase in the severity of most of her symptoms, but early in October 1945 she experienced a definite remission and found it possible, at last, to follow the advice of her doctor to seek specialist treatment in a capital city. This involved a two and a half days' journey, but accompanied by her husband, this was accomplished without incident. Treatment with prostigmin and ephedrine was commenced and the patient returned to the country where she entered a hospital in her home town. Because of the coexistent pregnancy however, she was transferred to the Brisbane General Hospital on 16th November, 1945, where I saw her in consultation shortly afterwards.

She presented a typical picture of myasthenia gravis with bilateral ptosis of the upper eyelids, slow deliberate movements and slurring of speech. She expressed the opinion that the weakness of her limbs and liability to fatigue was now less severe than formerly, but was concerned about her difficulty in swallowing. The uterus was enlarged to the size of a four and a half months' pregnancy. Treatment, which had been instituted immediately upon admission, consisted of the oral administration of 30 grains of prostigmin and 1½ grains of ephedrine three times a day, together with a daily combined injection of prostigmin 0.5 and 1/100 grain of atropine. A suitable diet was prescribed. Radiological examination of the superior mediastinum failed to reveal any abnormal shadows.

Subsequently, under this therapeutic *régime* steady progress was made towards improvement and the patient was admitted to the wards of the Brisbane Women's Hospital. The residual weakness in the limbs disappeared first but it was more than three weeks before the patient was able to swallow without difficulty. Consciousness of respiratory effort disappeared about the same time. Ptosis of the eyelids was the last manifestation to be relieved. However, in spite of this general improvement there was a tendency to occasional relapses lasting for three to four days, and the observation was made that these relapses corresponded closely to the times of the suppressed menstrual periods. They were characterized by drowsiness and a return of ptosis of the lids, dysphagia and slurring speech.

By the time the pregnancy had advanced to the 8th month the patient was considered to be well enough to leave hospital temporarily to stay with relations in the city. Treatment with prostigmin and ephedrine in the previous dosage was continued, the patient administering the hypodermic injection herself. Occasionally, through forgetfulness, she omitted to take the ephedrine or prostigmin tablets and found that she always suffered a minor relapse under these circumstances. There was no complaint of sleeplessness or excitement with the use of ephedrine in the dosage given. After 37 weeks gestation she developed a severe "cold" which appeared to precipitate a relapse lasting for a week with return of dysphagia and some degree of ptosis.

She re-entered hospital and subsequently remained in good health, labour pains commencing on the morning of 28th March, 1946. Acting on a previous decision, a combined injection of prostigmin (0.5 mg.) and atropine (gr. 1/150) was now given every 8 hours. In addition 0.1 mg. of prostigmin was given at the beginning of the second stage of labour. The blood group of the patient had previously been determined; she was found to be Group A, and Rh negative. Appropriate cross-matching with a selected sample of Group O. Rh negative blood from the blood bank demonstrated complete compatibility. By 6.30 a.m. on 29th March, i.e. just 24 hours after the onset of labour pains, the cervix was fully dilated with the membranes still bulging. These were ruptured artificially and the head was found to have reached the mid pelvis and to be lying in a position of deep transverse arrest.

Contractions, which had been of good quality during the earlier part of the night, had become a little weaker during the hour or two preceding this

examination. Following on the release of the forewaters however, their strength returned and three-quarters of an hour later, under anaesthesia, the occiput was rotated anteriorly without difficulty and a healthy female infant weighting 6 pounds 10 ounces was delivered with the use of forceps. Sedation during the course of labour had been effected by the administration of morphine sulphate gr. 1/6, hyoscine hydrobromide gr. 1/100 and atropine sulphate gr. 1/180, followed, towards the end of the first stage, by gr. 6 of sodium amytal. At no stage did the patient complain of undue fatigue. However, trouble developed during the third stage of labour in the form of a moderate but persistent postpartum haemorrhage. The placenta was therefore expressed by Crede's manoeuvre and ergometrine (0.125 mg.) was administered intravenously. Effective haemostasis was obtained in this way and the general condition of the patient was entirely satisfactory when subsequently transferred from the delivery room to a lying-in ward.

Three hours later she began to tremble persistently but not violently. This was accompanied by general emotional instability. The attack lasted for approximately half an hour and was the only occurrence of this character. The trembling was ascribed to the extra amount of prostigmin administered during the labour. Subsequently she expressed the opinion that she felt quite as well as before the confinement and throughout the remainder of her stay in hospital relapse of any kind did not occur. A blood transfusion was given on the third day of the puerperium and the previous dosage of prostigmin and ephedrine was maintained. The patient left hospital on the 15th day and was seen at the post-natal clinic a month later when she reported having had a short relapse some two weeks previously.

The baby was being fully breast fed but the mother noticed that she became very tired and felt " as though she wanted to go to sleep on her feet," if, through pre-occupation, she missed the proper time for taking the tablets. Seen again a month later, on the eve of her return to the country, entirely favourable progress was reported. In reply to a letter sent after a further interval of two months it was learned that no major relapse of any kind had occurred.

## Discussion.

The *rôle* of acetylcholine as a chemical transmitter of parasympathetic impulses is now clearly established, as also is the presence of a blood esterase for its destruction. It is presumed that in myasthenia gravis there is either an insufficient amount of acetylcholine or an increase in cholin esterase. Actual determination of the esterase content of the blood in myasthenia gravis has given conflicting results[6] and, not infrequently, is found to be within normal limits. Kennedy and Wolf[7] are not prepared to accept this conception of the aetiology of the disease and believe that the lactic acid content of muscle in myasthenia gravis is diminished as a result of some metabolic disturbance. This had the effect of neutralizing the transfer of neural impulses, dependent on acetylcholine which, in turn, is ineffective in too low an acid, a neutral or an alkaline medium. Although the ultimate biochemical changes occurring in myasthenia gravis are as yet undetermined, an improvement in the clinical condition of the patient coinciding with a prostigmin-induced fall in blood esterase level is a constant finding.

As a consequence of the considerable period of time spent in hospital, it was possible closely to observe the clinical course of the condition presented by this case during the last $4\frac{1}{2}$ months of her pregnancy. In addition she was able to give a good account of the subjective manifestations noted during the earlier stages of her illness; *viz.* from June 1944 until November 1945. In this regard it would seem apparent that the condition had progressed to one of considerable severity prior to the institution of treatment with prostigmin and ephedrine and her subsequent favourable progress, in the presence of a co-existent pregnancy, is perhaps more significant for this reason.

The aggravation of symptoms prior to and during menstruation was particularly

noticeable in this case and the consistency with which this observation is made would further tend to disprove any suggestion that pregnancy may be a factor in precipitating the onset of the disease. This tendency for the patient to suffer a relapse at the time of menstruation has been put forward as evidence in favour of an endocrine disorder having an aetiological *rôle* in myasthenia gravis. Milhorat[8] however, whilst commenting on this phenomenon, and whilst finding that the effective dose of prostigmin often has to be increased during menstruation, considers that the aggravation of symptoms has no aetiological significance. He believes that the association is of the same order as that observed in certain other clinical conditions, especially those in which muscular disability exists, the symptoms of which are usually increased during menstruation.

In studying the effect of pregnancy on the course of myasthenia gravis from the clinical record of this case it is to be noted that the first rational and effective plan of treatment made available to her coincided with the last $5\frac{1}{2}$ months of the gestational period. Although a definite aggravation of symptoms developed during the first 3 months there was more than a suggestion of a spontaneous remission at the beginning of the second trimester and before the commencement of appropriate treatment. It was at this stage that a long and trying railway journey was successfully undertaken.

During the remainder of the pregnancy the clinical picture was one of steady improvement, punctuated by short-lived relapses at the times of the suppressed menstrual periods. The possibility of a "functional element" in these periodic relapses was considered (in view of the patient's previous experience in this regard) but objective as well as subjective phenomena were present in the form of a return of slight ptosis and loss of distinctness in speech at these times. The only other relapse throughout the pregnancy appeared to have been precipitated by an upper respiratory tract infection.

The onset of definite labour pains was gradual and permitted an increased dosage of prostigmin and atropine to be administered by 8-hourly injections. The total duration of labour ($24\frac{3}{4}$ hours) was in no way excessive in view of the primiparity of the patient, the gradual development of first stage contractions and the posterior position of the occiput. The reduction in the strength of uterine contractions towards the end of the first stage and in the early part of the second stage as well as the tendency to postpartum haemorrhage obviously point to the development of some degree of uterine exhaustion. But it is equally clear that this development was in no way a consequence of the myasthenia gravis. Deliberate rupture of the bag of forewaters at a slightly earlier stage might have been practised with advantage.

The presence of a complicated labour in a patient suffering from myasthenia gravis gives added significance to considerations governing the mode of delivery of these cases. For if, as would appear, Caesarean section is to go the way of therapeutic abortion in the management of these patients and the prostigmin-controlled cases considered essentially suitable for natural delivery, purely obstetrical complications are bound to develop from time to time. Should these manifest themselves before the onset of labour (cephalo-pelvic disproportion for example), their presence would rightly favour a decision to retain Caesarean section as the method of choice for delivery. But should such complications develop during the course of labour there is reason to believe that the management of the prostigmin-controlled case would give no undue cause for anxiety.

## Summary and Conclusions.

1. The present position in regard to the management of pregnancy and labour when complicated by myasthenia gravis is briefly discussed.

2. A case record is presented describing the clinical course of pregnancy, labour and the puerperium in a patient the subject of a previously untreated and severe form of myasthenia gravis.

3. Except for an aggravation of symptoms at the onset and transient mild relapses of a periodic nature, the pregnancy was uneventful and at no stage was the need for termination of the pregnancy even contemplated.

4. In spite of the labour being complicated by a posterior position of the occiput, there were, during this stage, no untoward developments which might have been attributed to the myasthenia gravis. Nor was there any evidence of undue fatigue of the voluntary musculature.

5. Although no serious relapse occurred during the puerperium, reduction in the daily dose of prostigmin and ephedrine could not be effected without a return of symptoms.

Acknowledgments are due to Dr. Clive Sippe, senior part-time physician to the Brisbane General Hospital, at whose request I undertook the care of this patient.

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# ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

A special meeting of the Council was held on Friday, September 27th, and an ordinary meeting was held on Saturday, September 28th, 1946, at the College House, with the President, Mr. Eardley Holland, in the Chair.

The Honorary Fellowship of the College was conferred on Mr. Victor Bonney in recognition of his work as a gynaecologist.

The following were formally admitted to the Membership by the President:

Hugh Rose Arthur
Samuel James Barr
Bryce Evans Blair
Catherine Isobel Blyth
Joyce Burt
Harold Burton
Guy Beadon Walmesley Fisher (*in absentia*)
Robert Leighton Hartley
Derek Jefferiss
Iola Lloyd Trevor Jones
Leslie Wallace Lauste
Margaret Orford
Hedley Charles Perry
Dwijendra Lal Poddar
Esther Mary Pollock
James Edmund Scott-Carmichael
Eric Wilfred Lowther Thompson
Thomas George Edward White

At the termination of the meeting of the Council held on Saturday, 28th September, Mr. William Gilliatt, London, assumed the Office of President, Sir William Fletcher Shaw, Manchester, and Mr. James M. Wyatt, London, assumed the Offices of Vice-President, and Mr. Arthur A. Gemmell, Liverpool, assumed the Office of Honorary Treasurer.

# INDEX TO CURRENT LITERATURE

In this Index an endeavour will be made, so far as conditions permit, to maintain an up-to-date record of all titles bearing on obstetrics and gynaecology and the infant. The classification aims at making immediately available for the reader the titles under the various subject headings. In the majority of instances the title is obtained from the original publication. Where this has been impossible, the title has been obtained from the abstracting journal shown in brackets. Reprints will be welcomed and should be sent to the Editor.

Any inquiries should be addressed to Miss D. F. Atkins, British Postgraduate Medical School, Ducane Road, London, W.12.


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